W1: Developmental Toxicology. Different Models, Different Endpoints
IUtox, Merida, MEXICO – Oct 3, 2016

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

DISCLAIMER: *The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.*

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 cell assay predicts 18% of the 1065 chemicals tested as positive for DevTox (~80 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

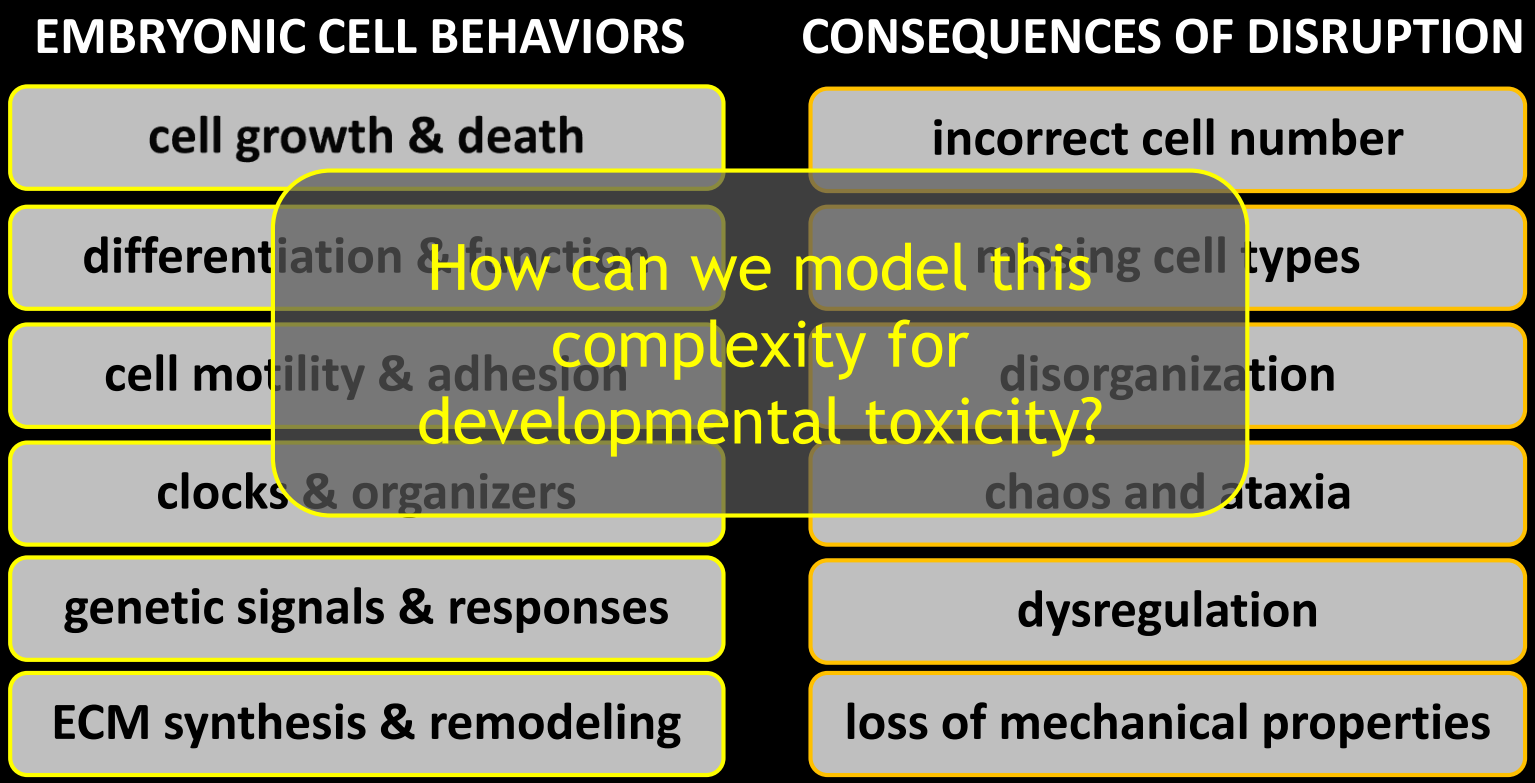
chemicals interact with biological systems wired for change

variation by species (e.g., thalidomide)

embryogenesis is critically dependent on cellular dynamics



Embryogenesis is an orchestration of complex cell behaviors

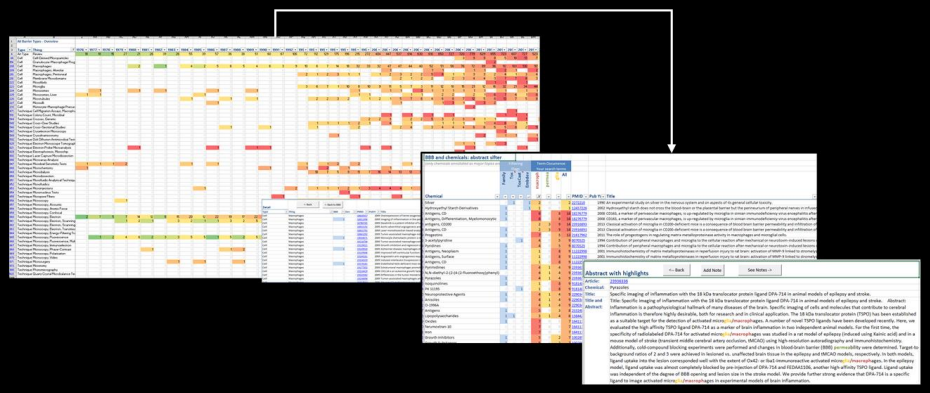


Using the new HTS data streams to model DevTox

- **Hypothesis:** computer models that recapitulate embryology can be used analytically (to understand) and theoretically (to predict) developmental hazards.

- **Approach:** design, development, and implementation of computational models that integrate toxicological data with knowledge of the embryo.

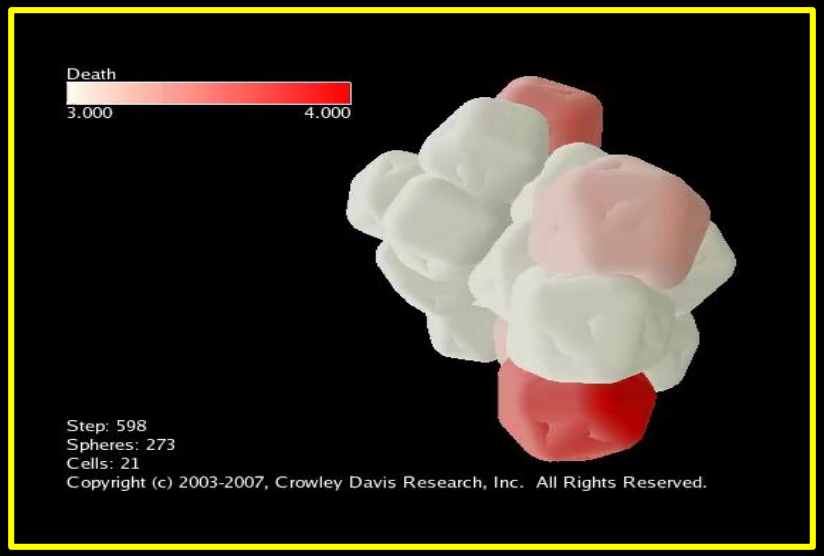
- **Application:** 'Virtual Embryo' - a novel way to predictively model the complexity of development for exposure-based hazard assessment.



Anatomical homeostasis in a self-regulating Virtual Embryo



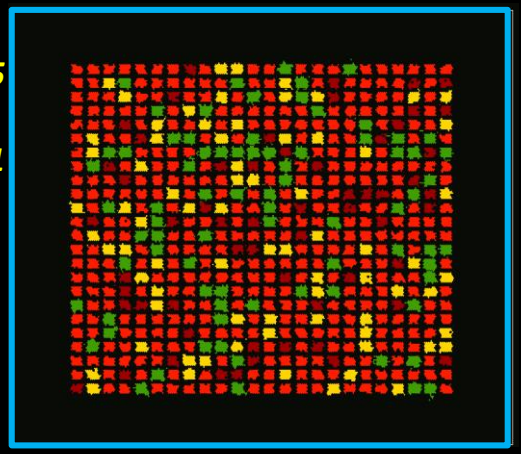
Mouse Morula
SOURCE: Science Photo Library

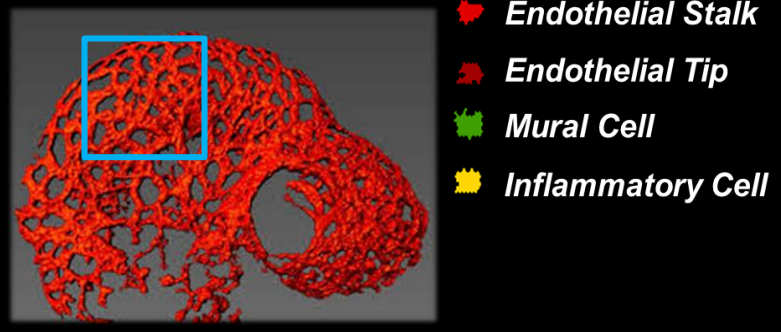


SOURCE: Andersen, Newman and Otter (2006) Am. Assoc. Artif. Intel.

Cellular Agent-Based Model

(angiogenesis)





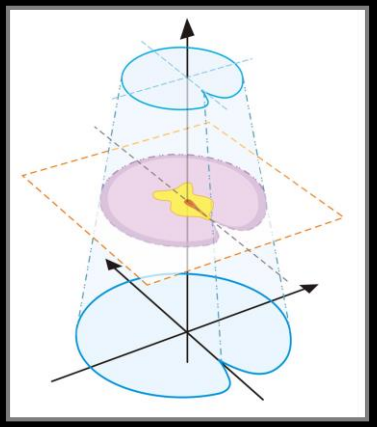
- CompuCell3D modeling environment (Indiana University – J Glazier)
- steppables for distinct cell behaviors (growth, proliferation, apoptosis, differentiation, polarization, motility, ECM, signal secretion, …)
- rules coded in Python for cellular 'agents' that have autonomy as individual models
- agents 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

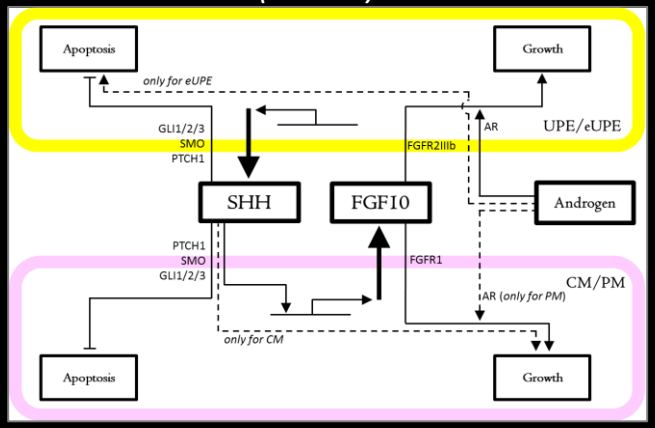
Embryonic GT



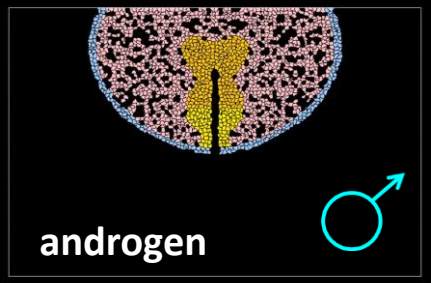
Abstracted GT

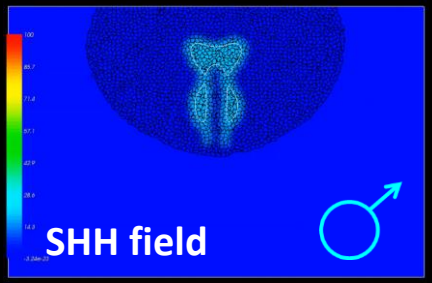


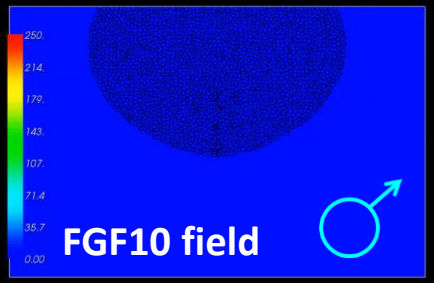
Control Network (mouse)



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



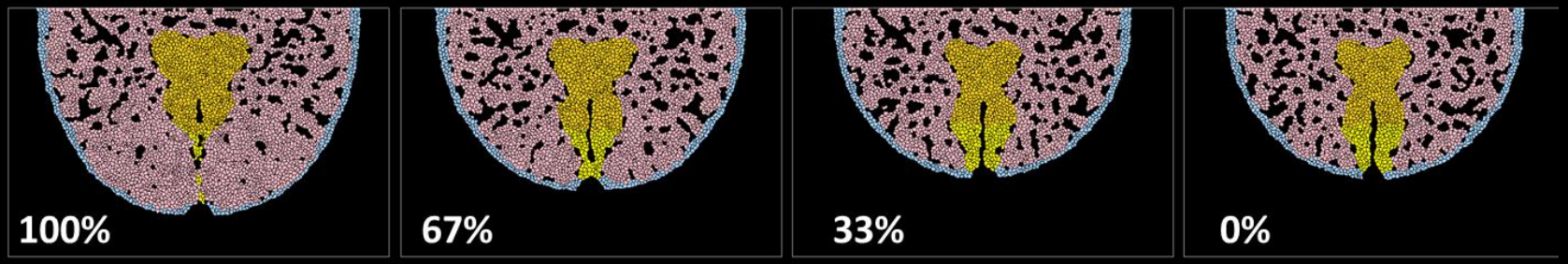






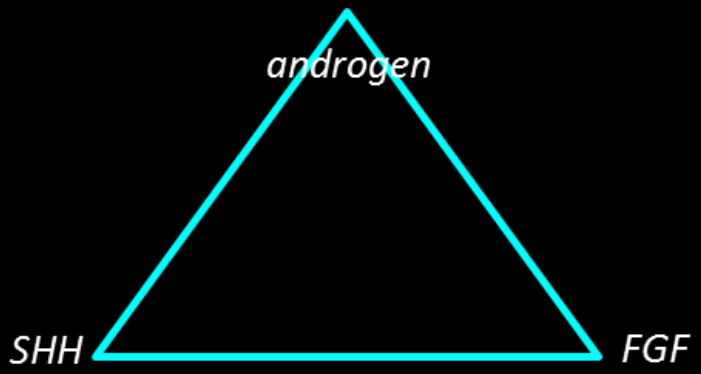
Urethral Closure: complex process disrupted in 'hypospadias'

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

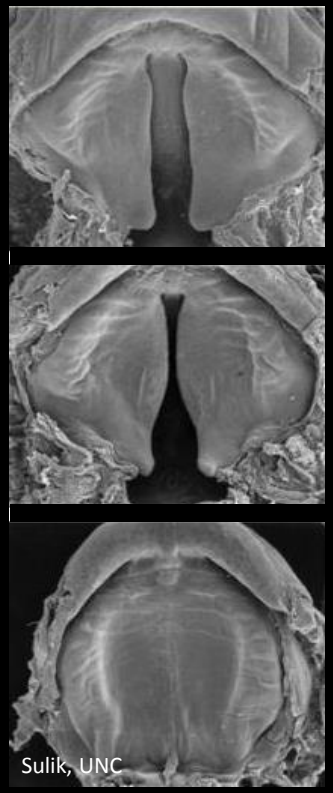


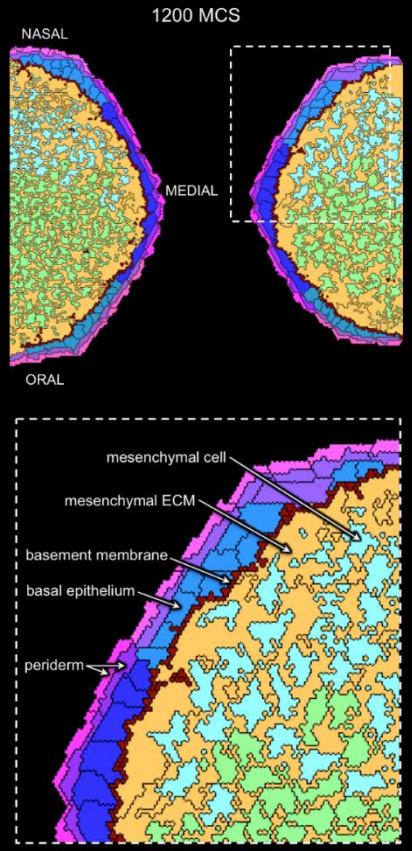
Leung et al. (2016) *Reproductive Toxicology*

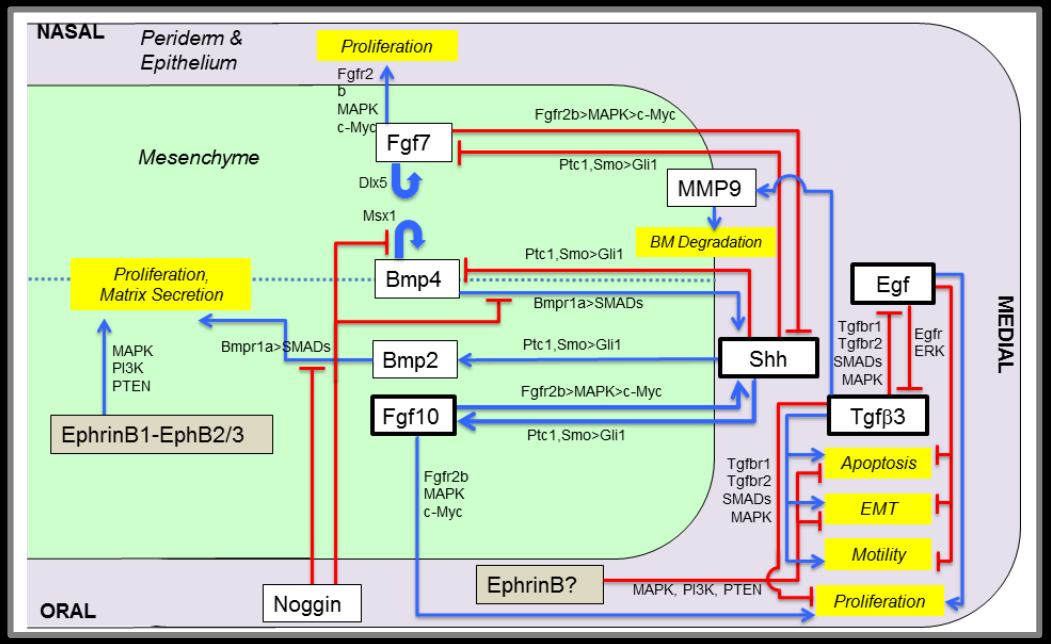
Androgenization	
(n = 10 sims)	Closure Index
100%	0.80
67%	0.57
33%	0.13
0%	0.07



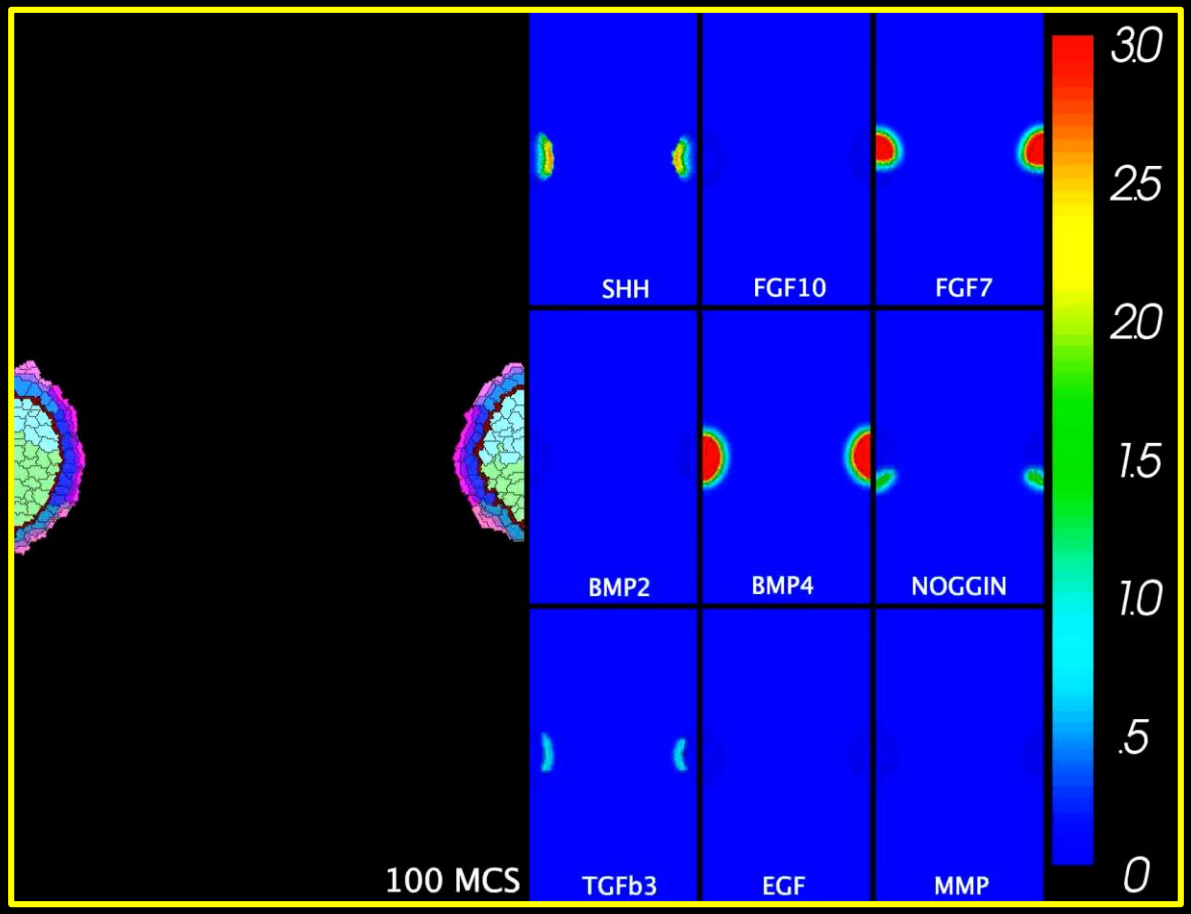
Virtual Palate Development: medial edge fusion



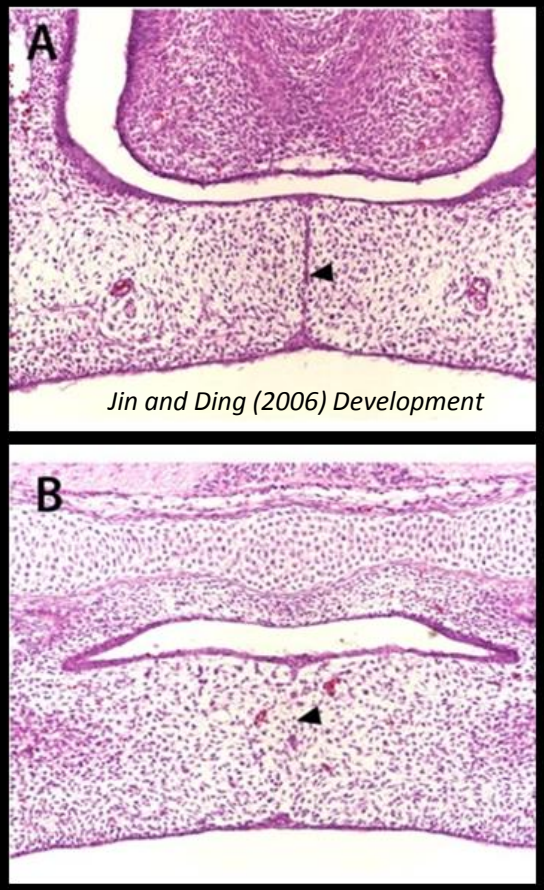




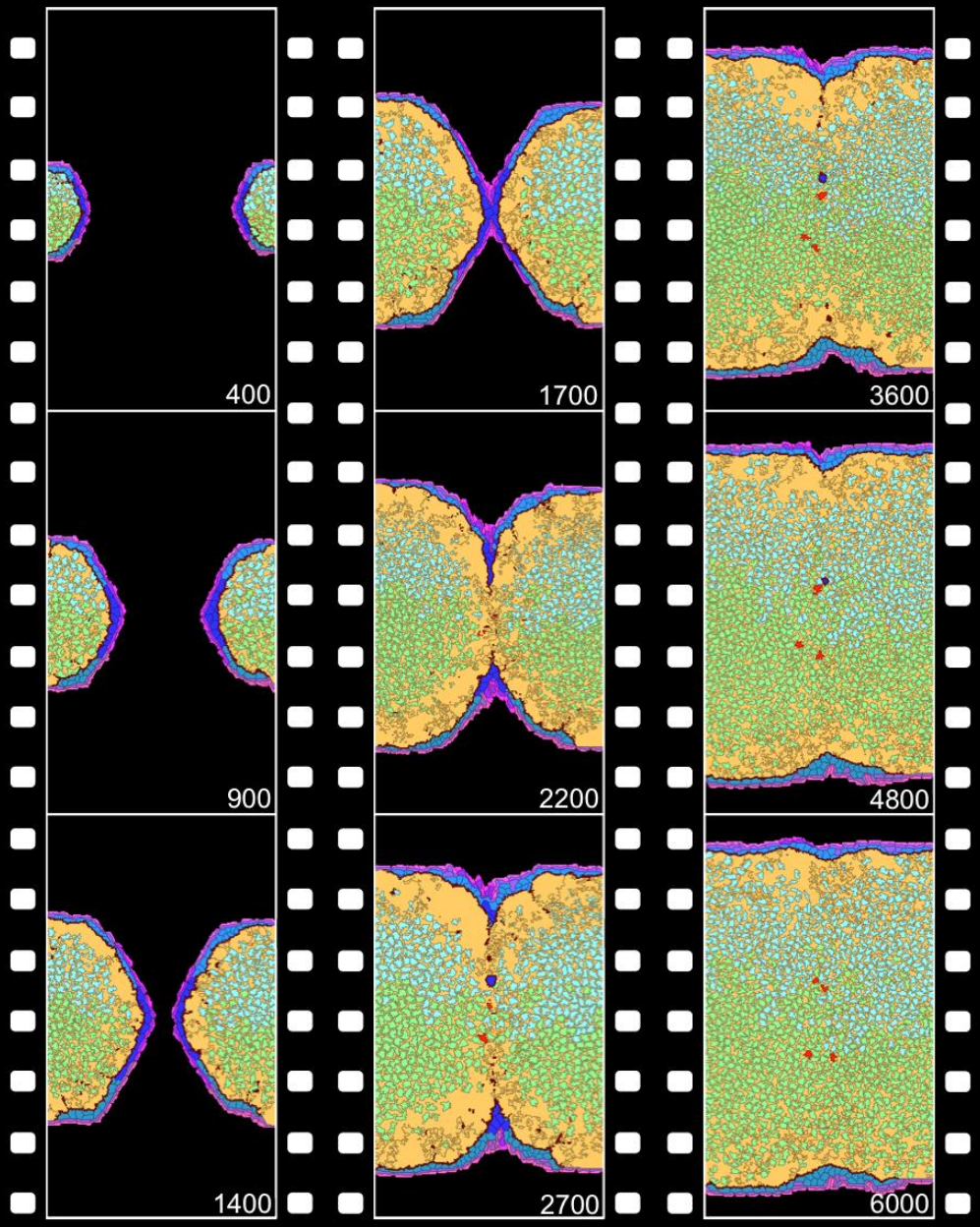
Hutson et al. (2016) submitted


SHH
FGF10
FGF7
BMP2
BMP4
NOGGIN
TGFb3
EGF
MMP
100 MCS
3.0
2.5
2.0
1.5
1.0
.5
0

ABM for Fusion

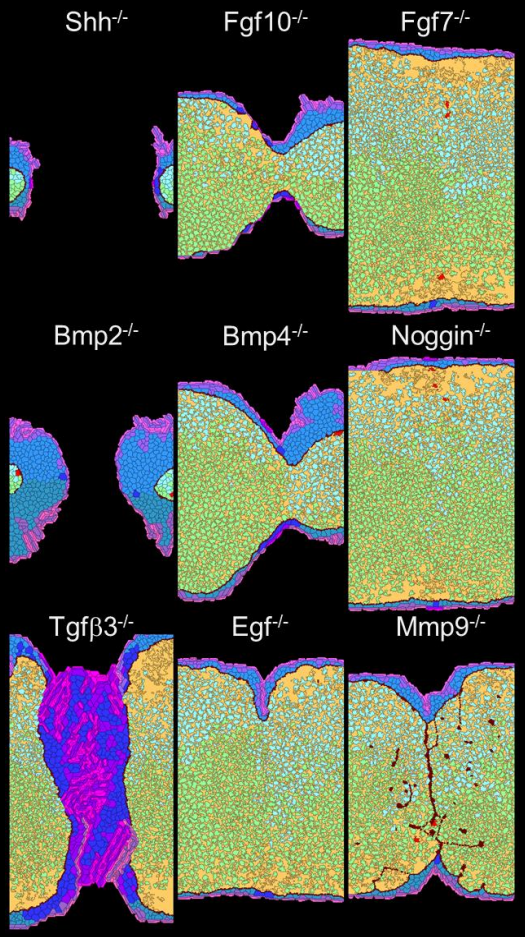


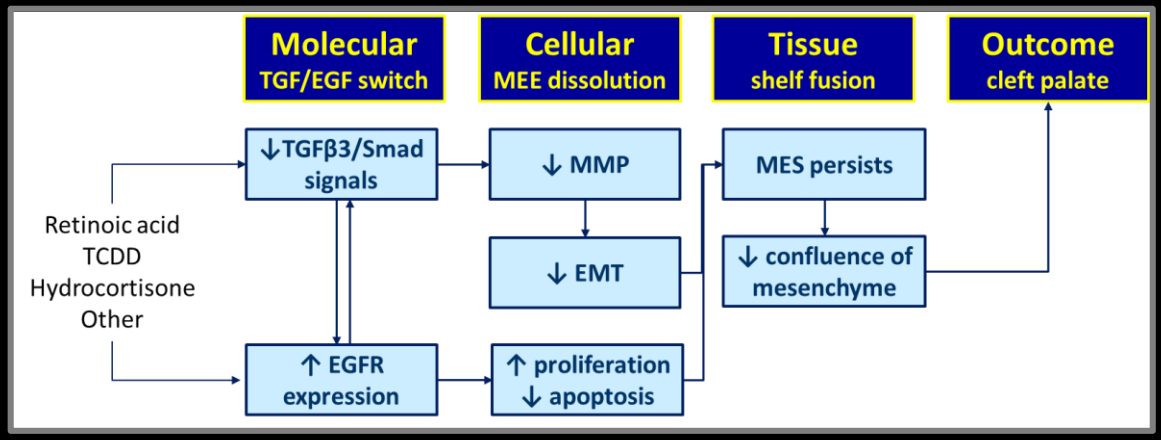
Jin and Ding (2006) Development



Hacking the Control Network:

in silico knockouts → Cybermorphs



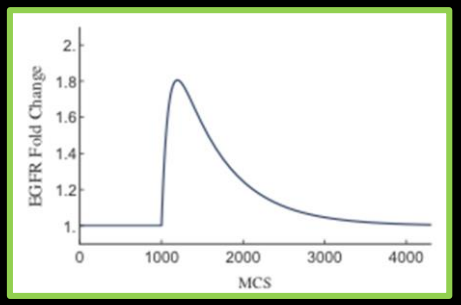


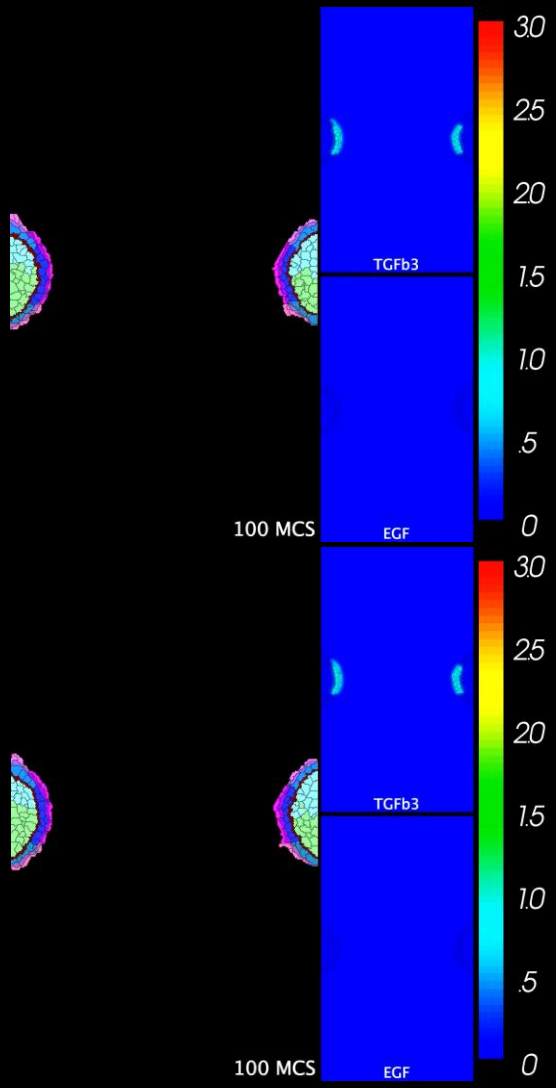
Fusion Switch

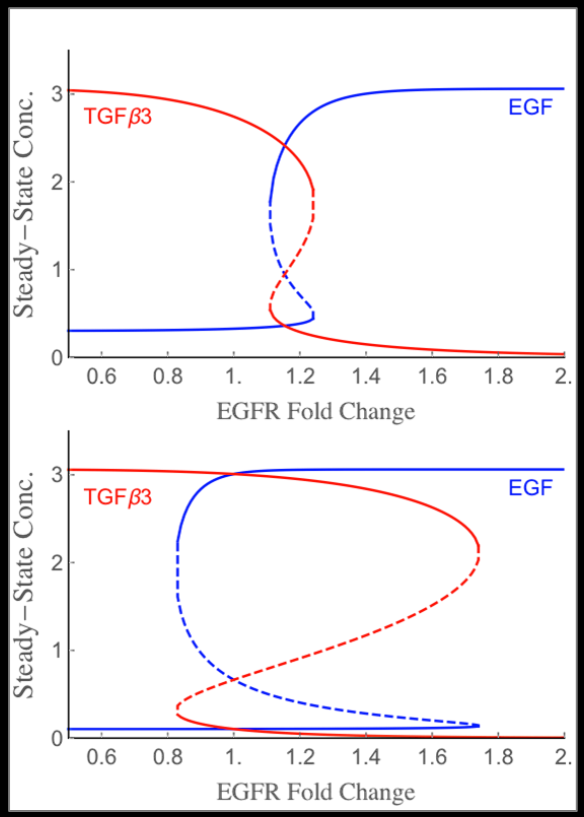
- TGFβ3 triggers apoptosis, epithelial-mesenchymal transition, and retraction to break down the midline seam.
- EGF has the opposite effect, maintaining epithelial proliferation and survival.
- ToxCast profiling for 63 cleft palate teratogens pointed to ~10 bioactivity clusters (eg, retinoid, glucocorticoid, GPCR, …).

TGF-EGF circuit dynamics:

modeling acute exposure to retinoic acid



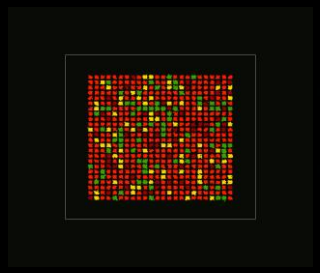


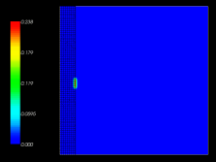


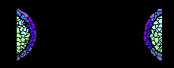
tipping point >1.8x (n=24)
(reversible)

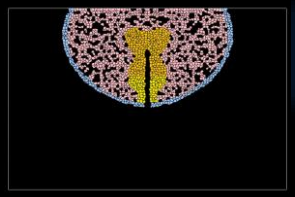
tipping point ~1.5x (n=16)
(non-reversible)

Toward a Virtual Embryo









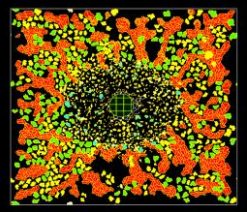
Vasculature

Limb-bud

Palate

Genital Tubercle

NVU/BBB



Heart

Neural Tube

v-Embryo™

Liver / GI

Testis / BTB

Renal

Underway

Planned

Future

Special Thanks

- Sid Hunter – NHEERL / ISTD
- Max Leung – NCCT (now NHEERL/ISTD)
- Nicole Kleinstreuer – NCCT (now NHEERL/NTP)
- Nisha Sipes – NCCT (now NHEERL/ISTD)
- Richard Spinnler – Leidos / NCCT
- 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



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



National Center for Computational Toxicology

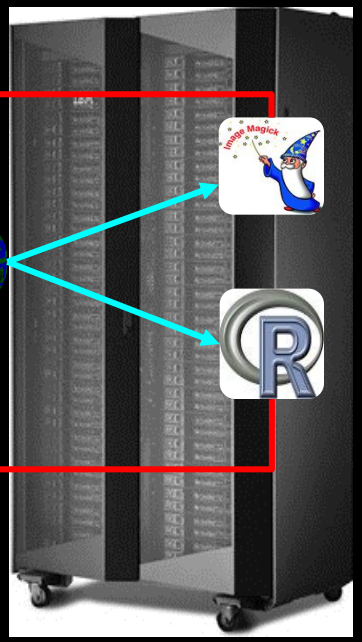
Virtual Tissues Laboratory System

VIRTUAL TISSUES
LABORATORY SYSTEM

Virtuoso
Web Services and Queries



HPC
Massively-parallel simulation

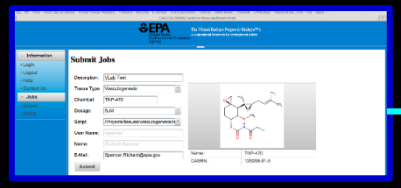


Video or 3D Results



VTKB
CC3D simulations
ToxCastDB
Bionetworks
Literature mining
Provenance

Data Analysis



BIO2RDF