Computer modeling and simulation to reconstruct the basis of developmental toxicity

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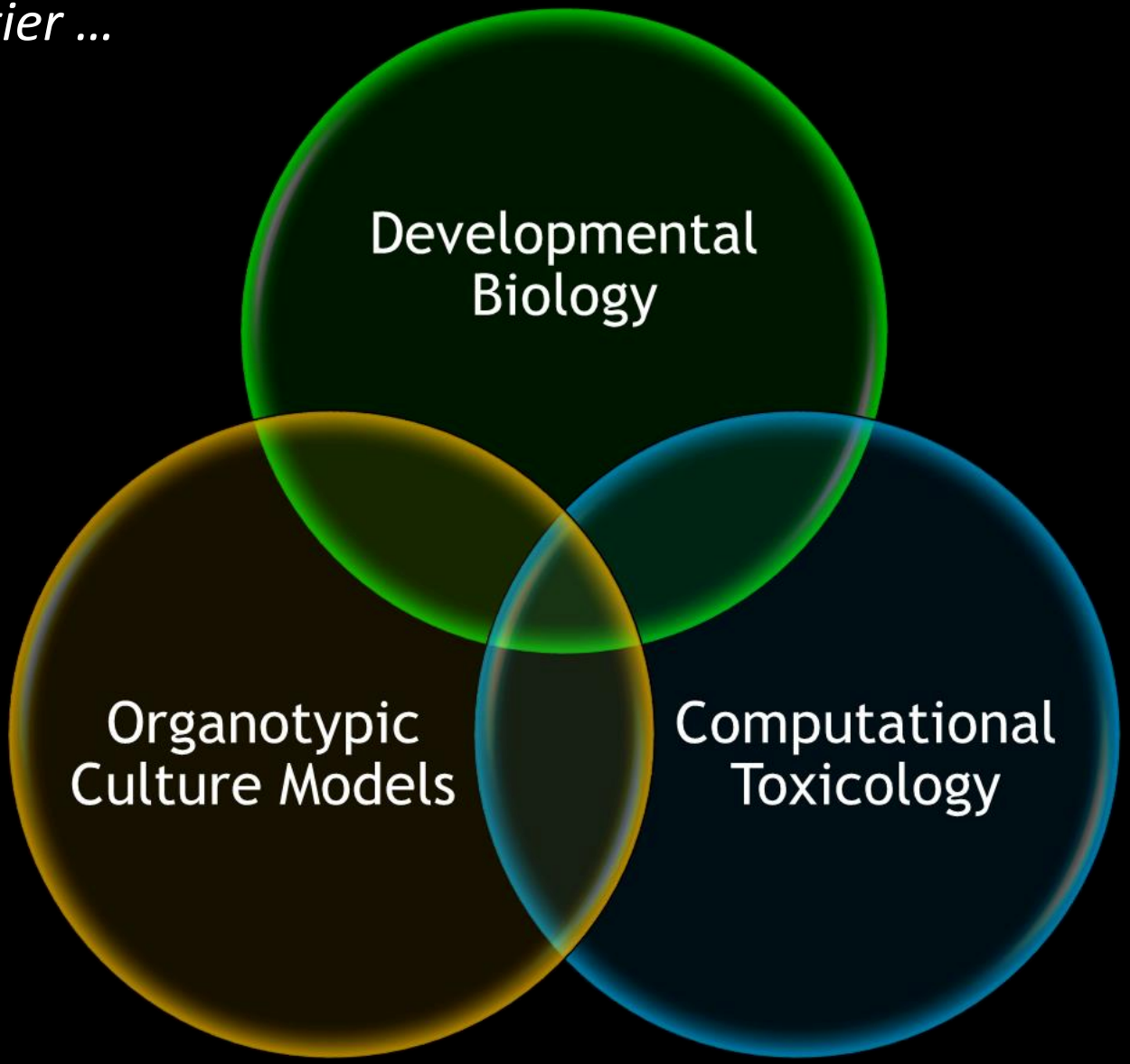
Problem statement

- Chemical exposure to a pregnant woman has the potential to affect her unborn child, leading to adverse birth outcomes and/or risks to early child development.
- Assessing developmental toxicity is commonly based on anatomical development of rat or rabbit fetuses exposed during pregnancy.
- Reauthorized TSCA (2016): EPA must accelerate development of scientifically valid test methods to prioritize large numbers of chemicals with less reliance on animal testing.
- 'Advancing actionable alternatives to vertebrate animal testing for chemical safety assessment' requires *in vitro* data and *in silico* models for complex processes.

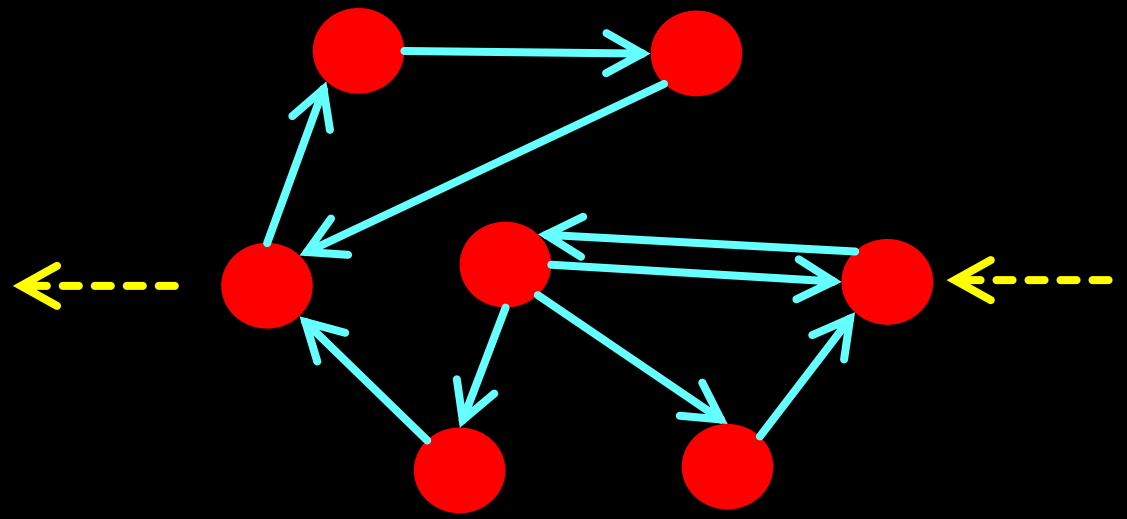
https://www.epa.gov/research-grants/research-funding-opportunities

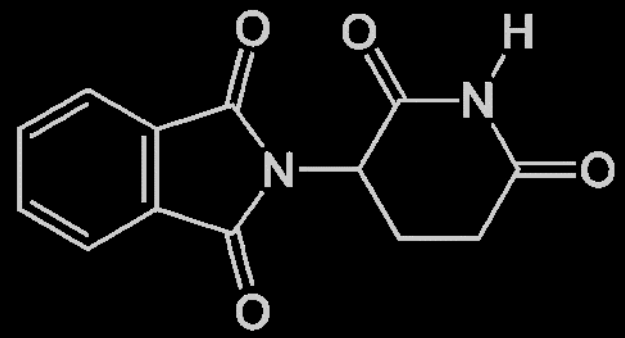
Funding Opportunity: EPA-G2018-STAR-C1, solicitation closing date September 25, 2018

Predictive Toxicology: *the final frontier …*



Computer modeling and simulation: uniquely positioned to translate data from *in vitro* cell and tissue models into higher-order topologies predicted for complex systems.

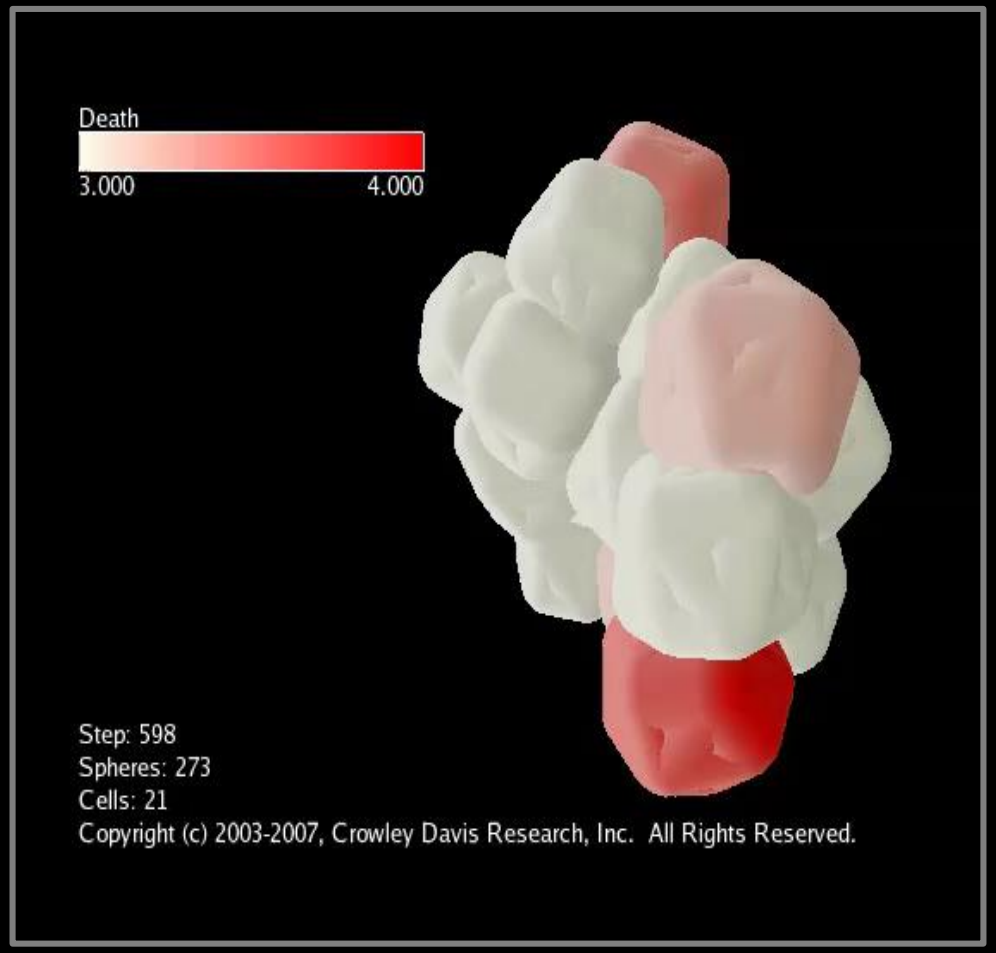




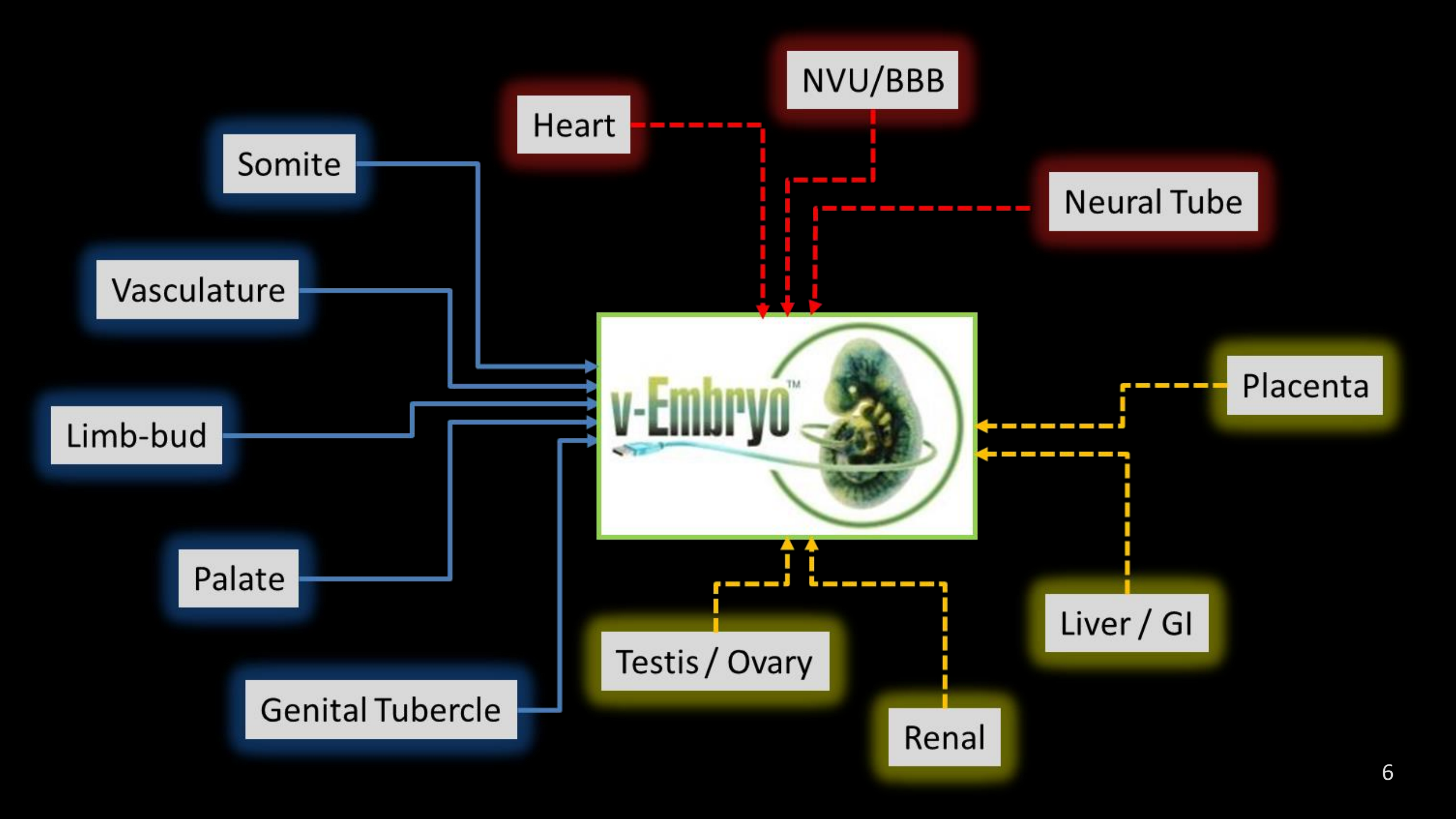
thalidomide

Self-organized cellular relationships

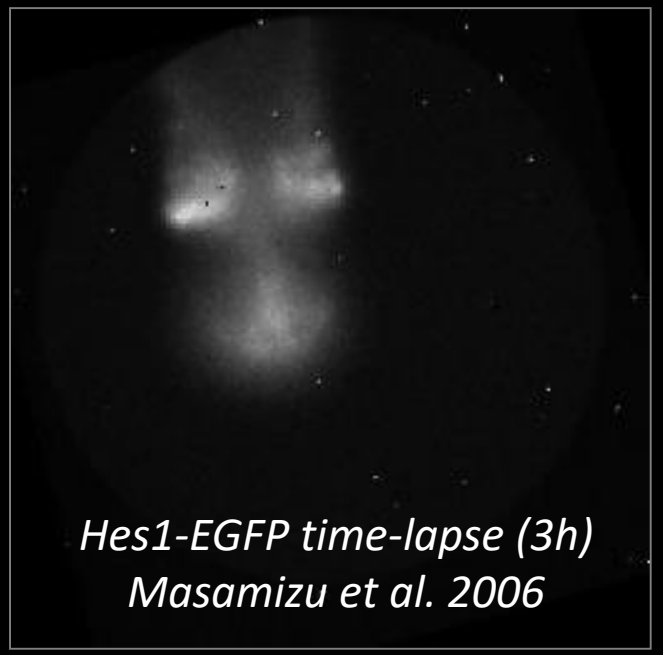
Anatomical homeostasis in a self-regulating ‘Virtual Embryo’



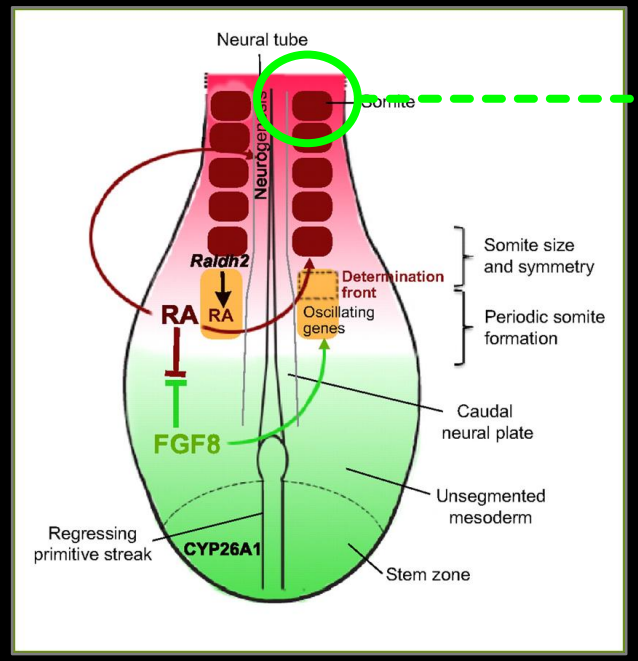
SOURCE: Andersen, Newman and Otter (2006) Am. Assoc. Artif. Intel.

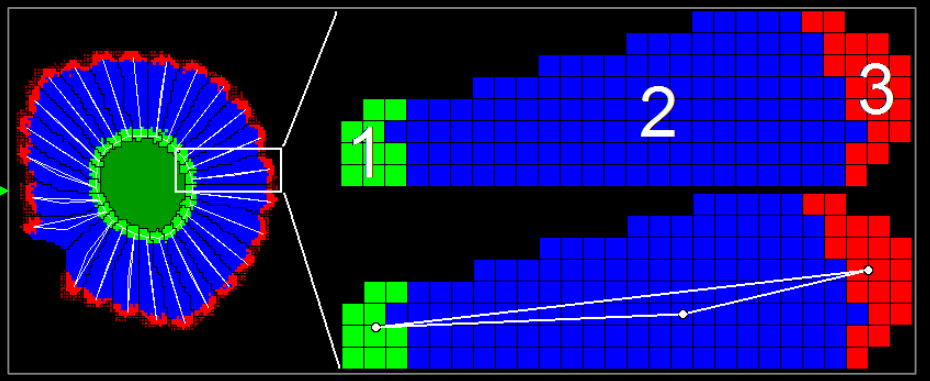

NVU/BBB
Heart
Somite
Neural Tube
Vasculature
v-Embryo™
Placenta
Limb-bud
Palate
Liver / GI
Testis / Ovary
Renal
Genital Tubercle

Modeling somite development



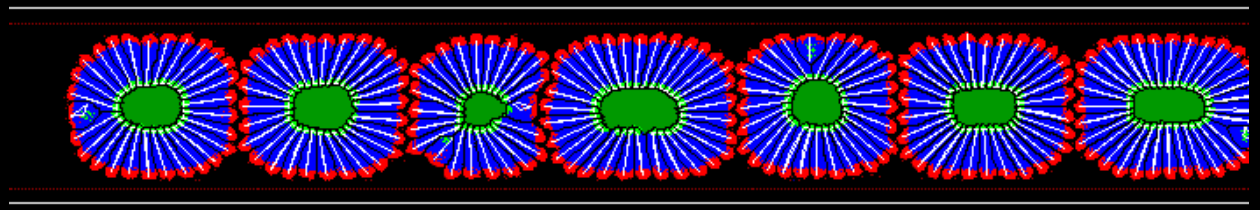
Hes1-EGFP time-lapse (3h)
Masamizu et al. 2006



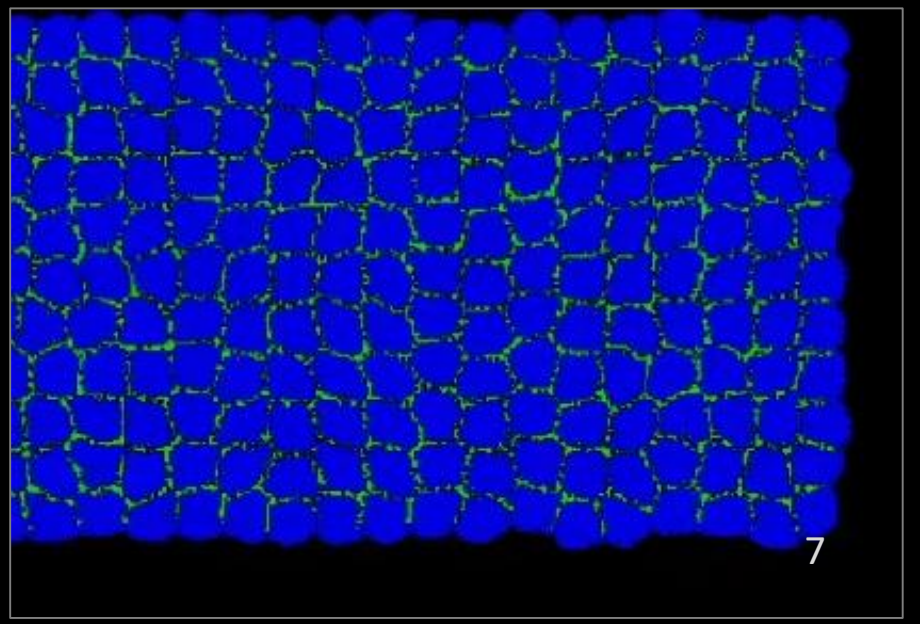


Differential cell adhesion

- *clock genes do not oscillate*
- *somites form simultaneously*

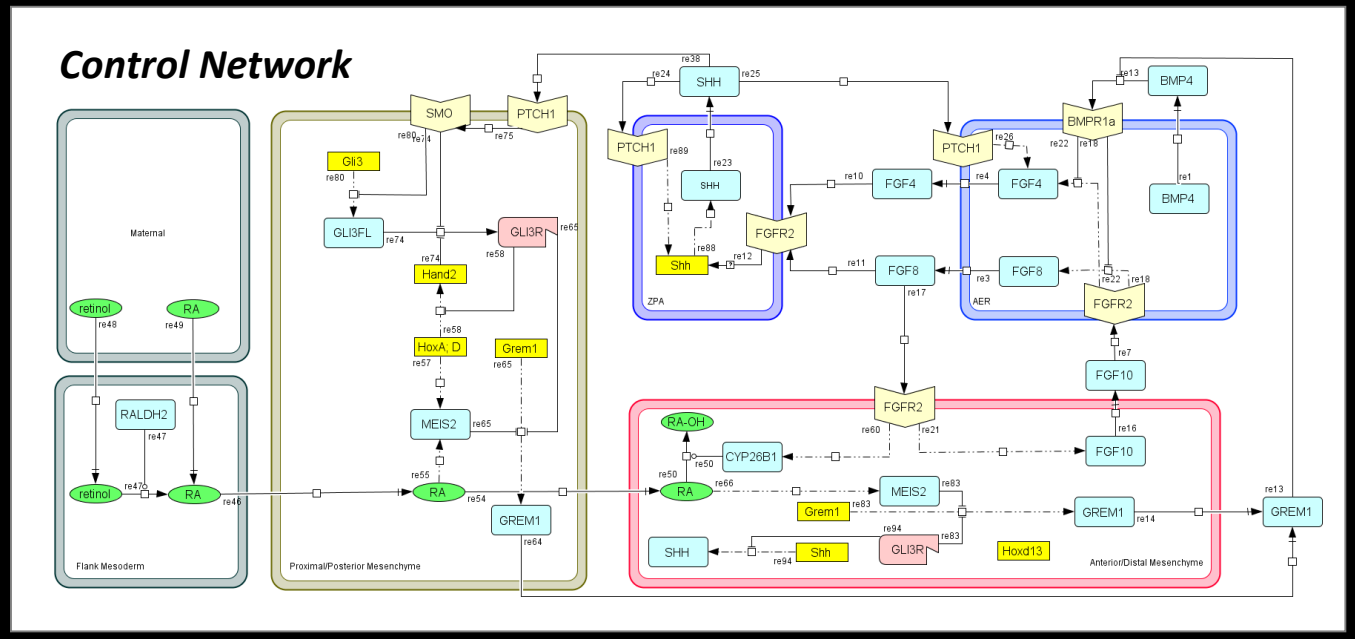


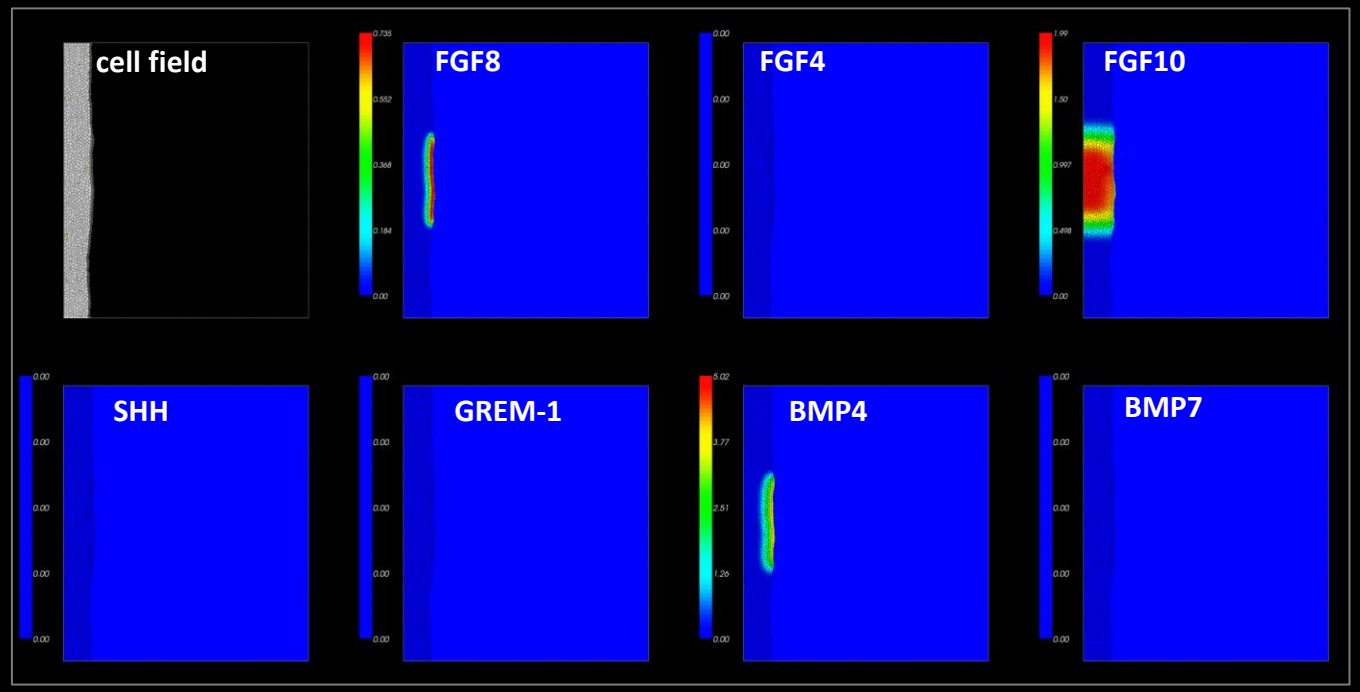
- *FGF8 wavefront restores sequentiality*
- *oscillatory clock improves regularity*

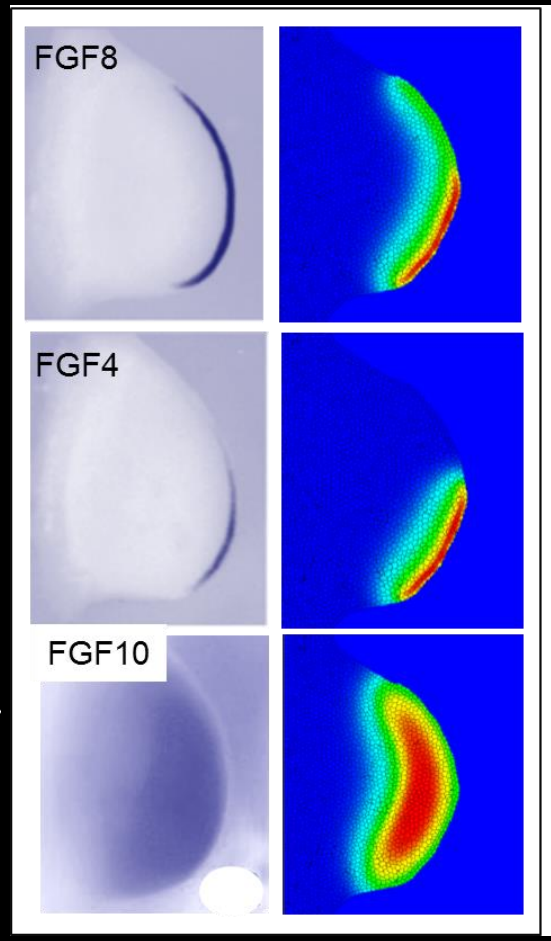


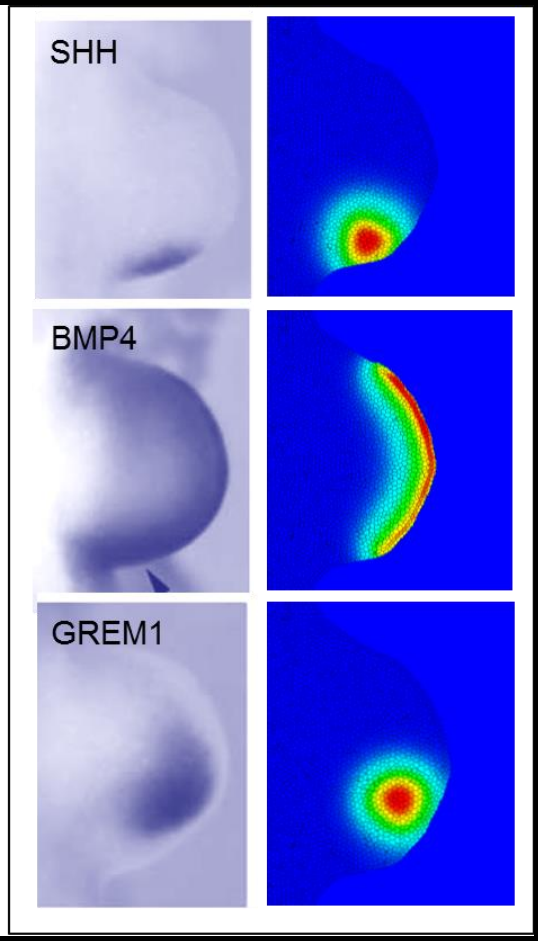
SOURCE: Dias et al. (2014) Science

Limb-bud outgrowth



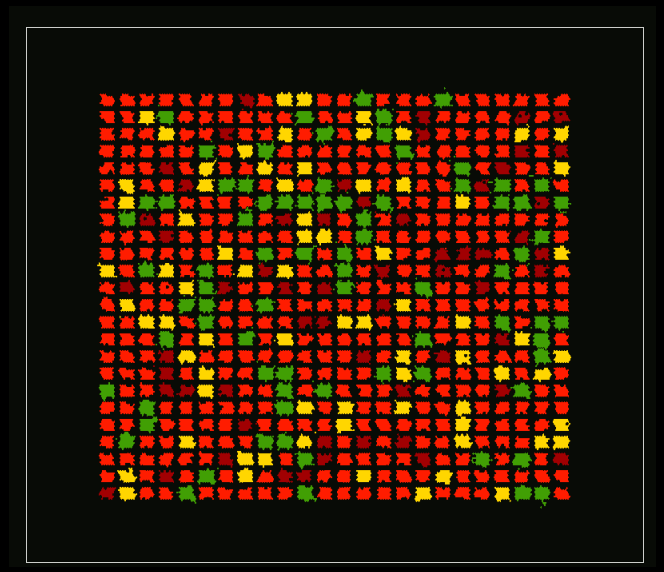






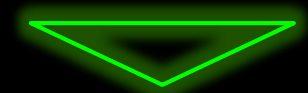
Modeling vascular development: the angiogenesis cycle

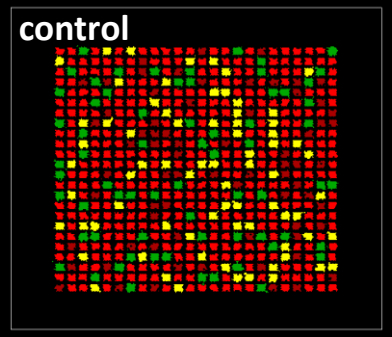
VEGF165
MMPs
VEGF121
sFlit1
TIE2
CXCL10
CCL2

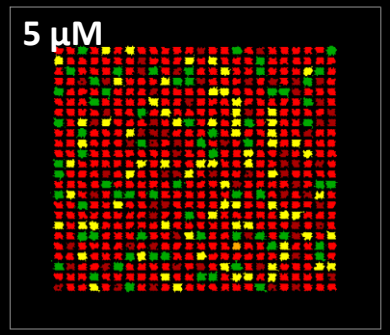


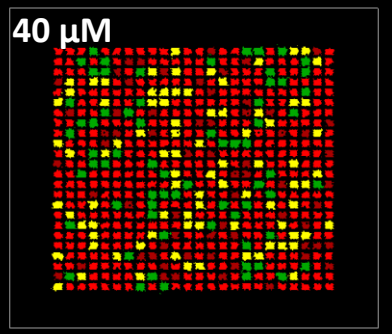
- *Endothelial Stalk*
- *Endothelial Tip*
- *Mural Cell*
- *Inflammatory Cell*

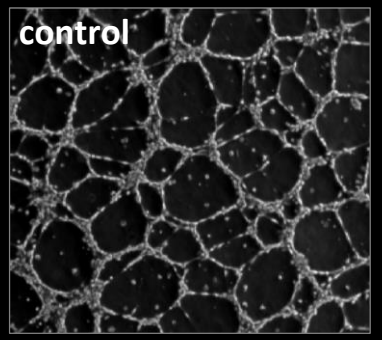
ToxCast bioactivity profile for 5HPP-33
(synthetic thalidomide analog)

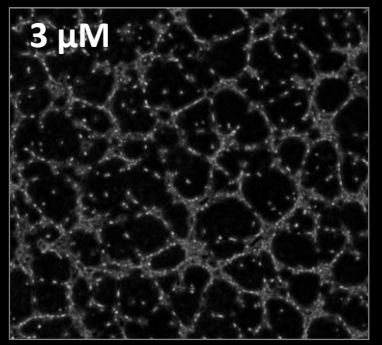


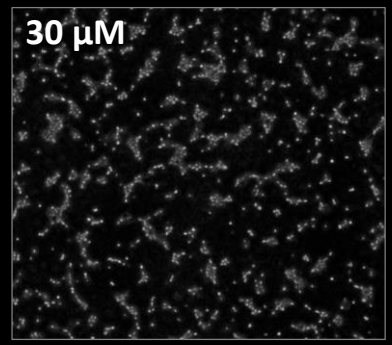










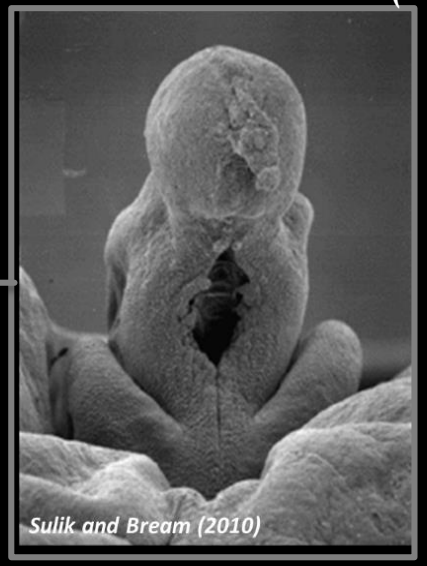


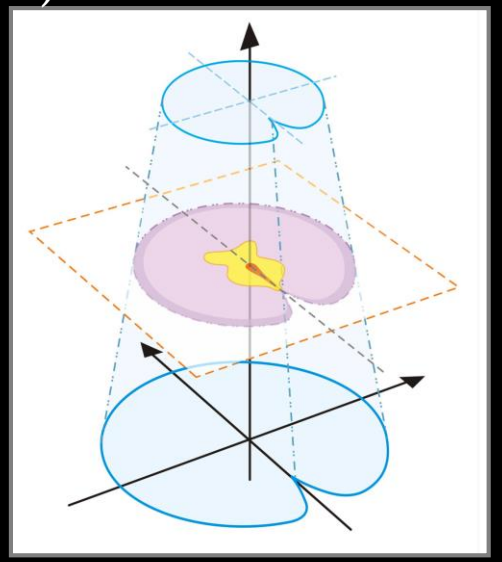
SOFTWARE: www.CompuCell3D.org
BioComplexity Institute, Indiana U

SOURCE: Kleinstreuer et al. (2013) PLoS Comp Biol 9(4): e1002996

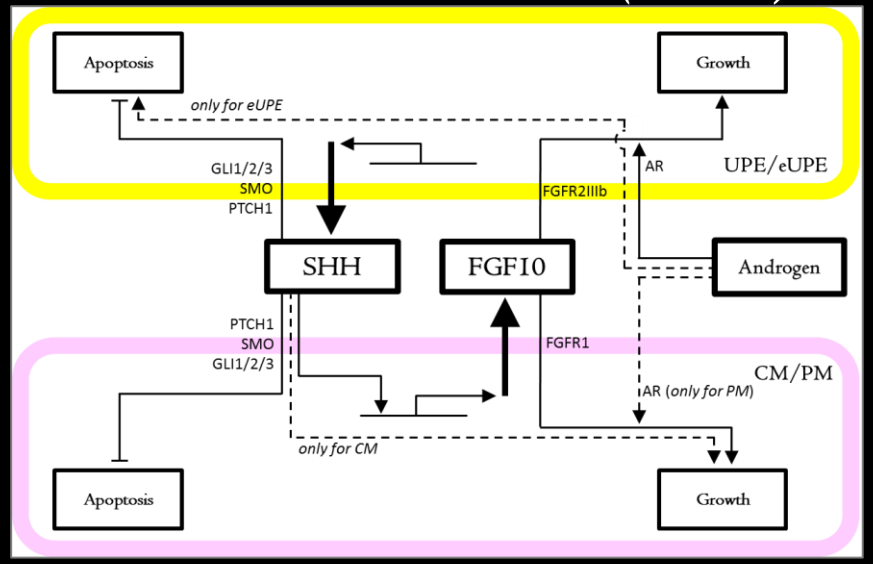
Sexual dimorphism: *genital tubercle morphogenesis*

Genital tubercle (GT)

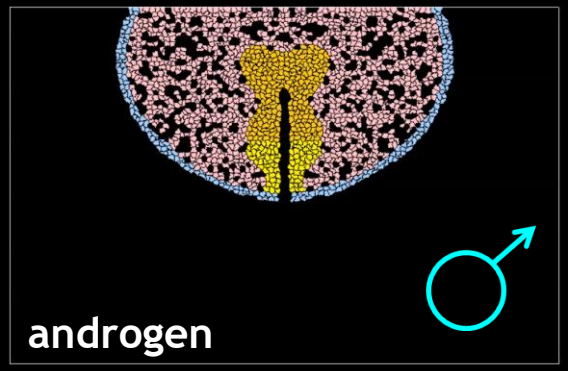


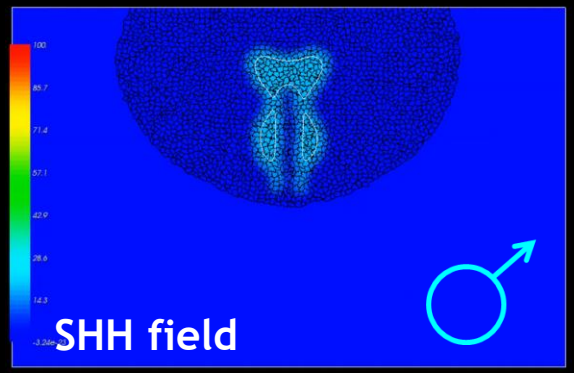


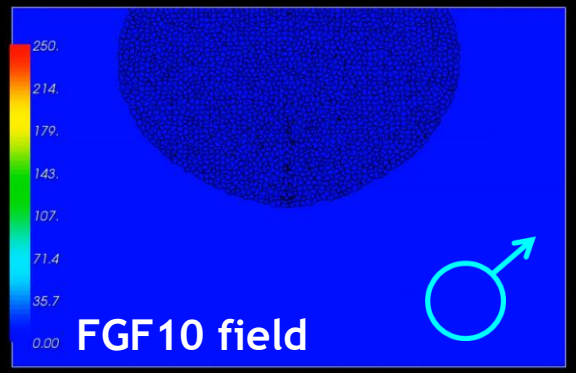
Control Network (mouse)



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

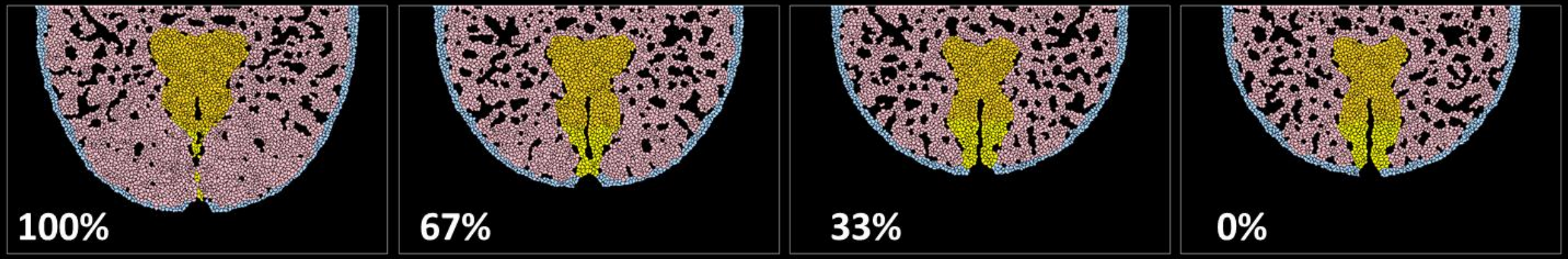


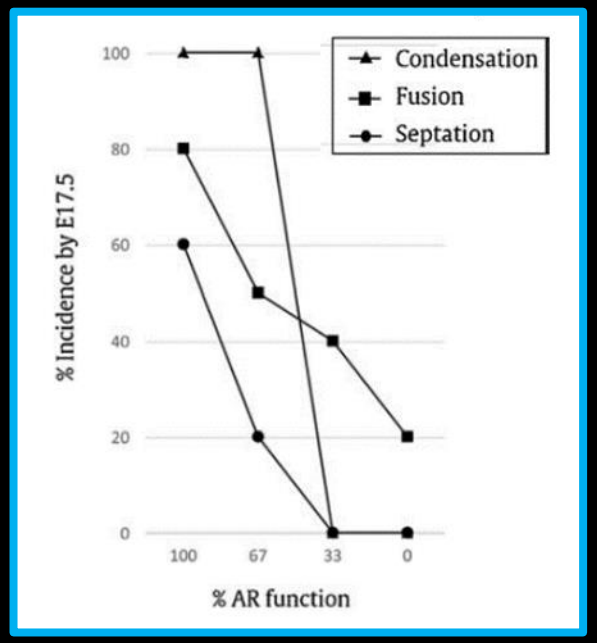




SOURCE: Leung et al. (2016) Reproductive Toxicology

Androgen virulization: *closure rates @4000 MCS ∫ androgen supply*

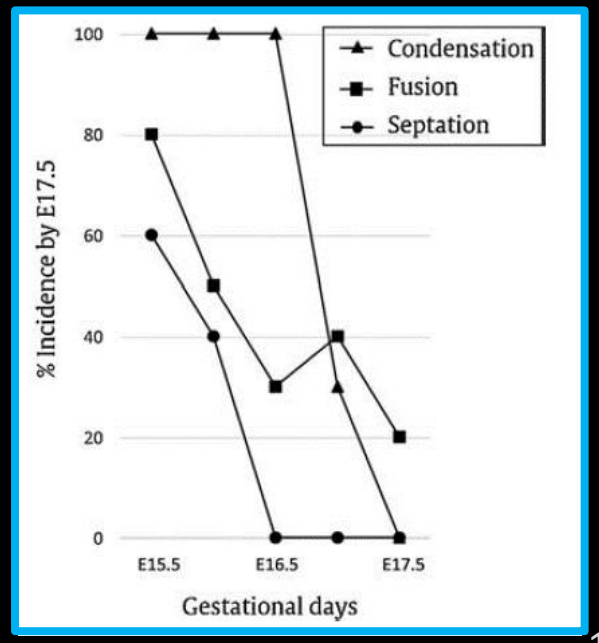




Closure indices (simulated, n=10)

LEFT: androgen insufficiency

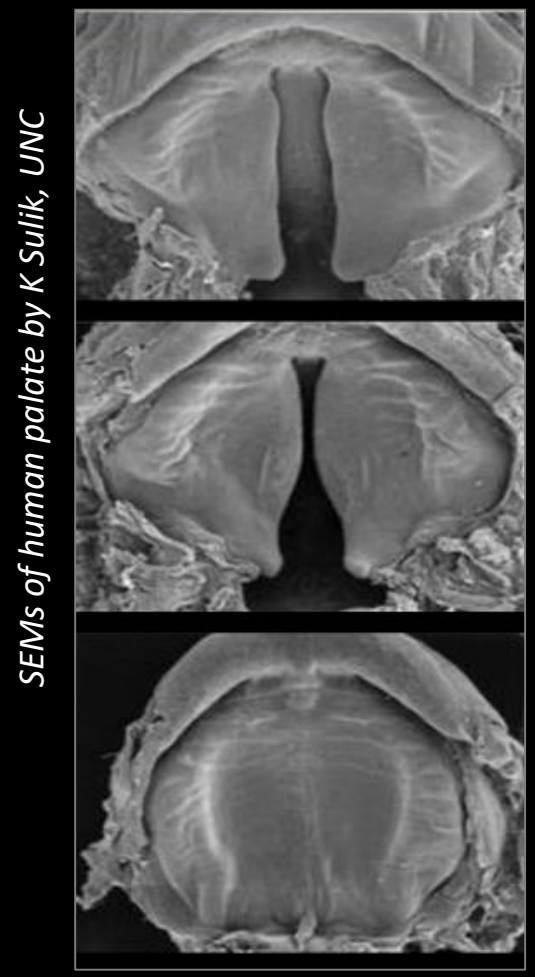
RIGHT: delayed virulization

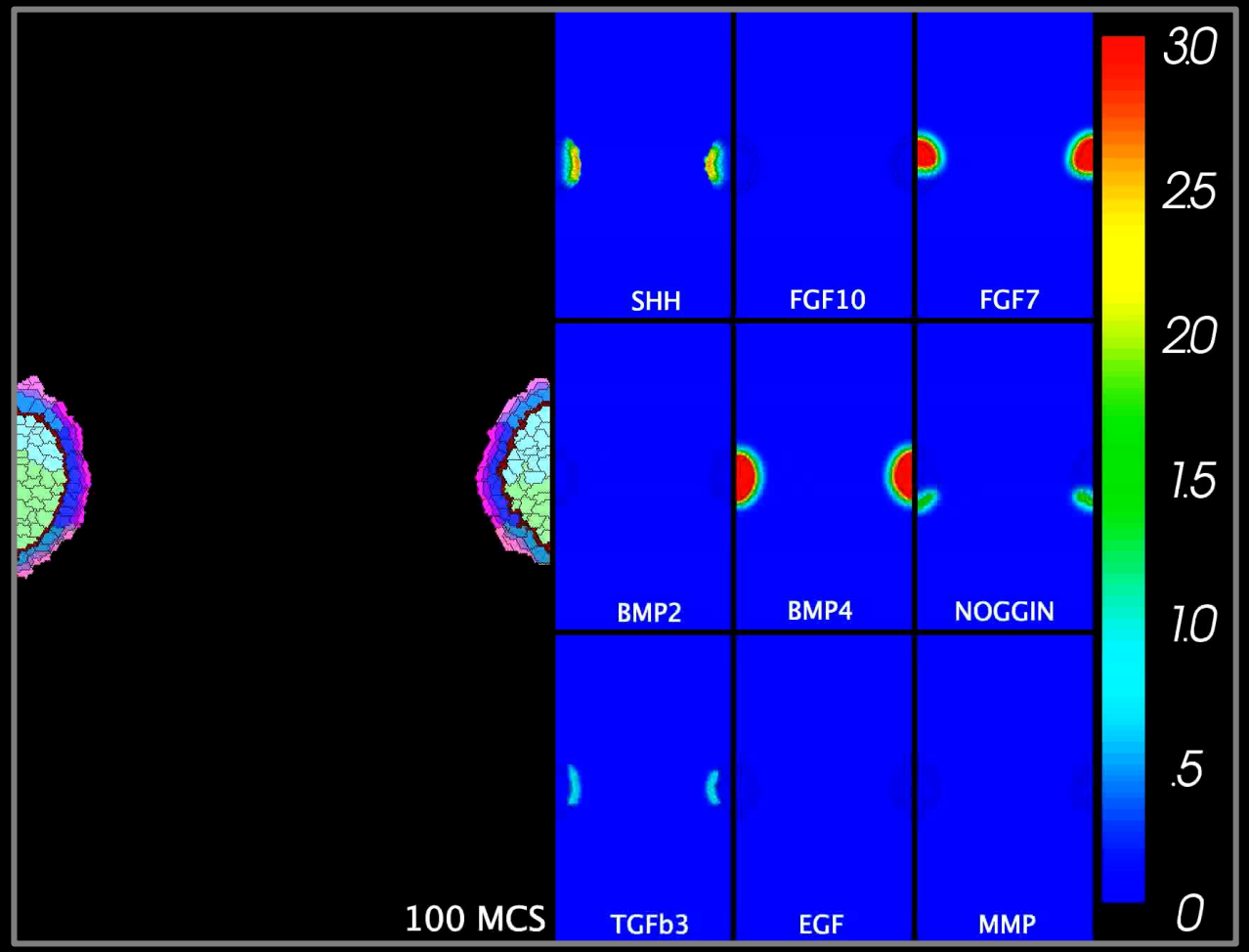


Palatal closure: *driven by medial edge epithelium (MEE) seam breakdown*

in vivo

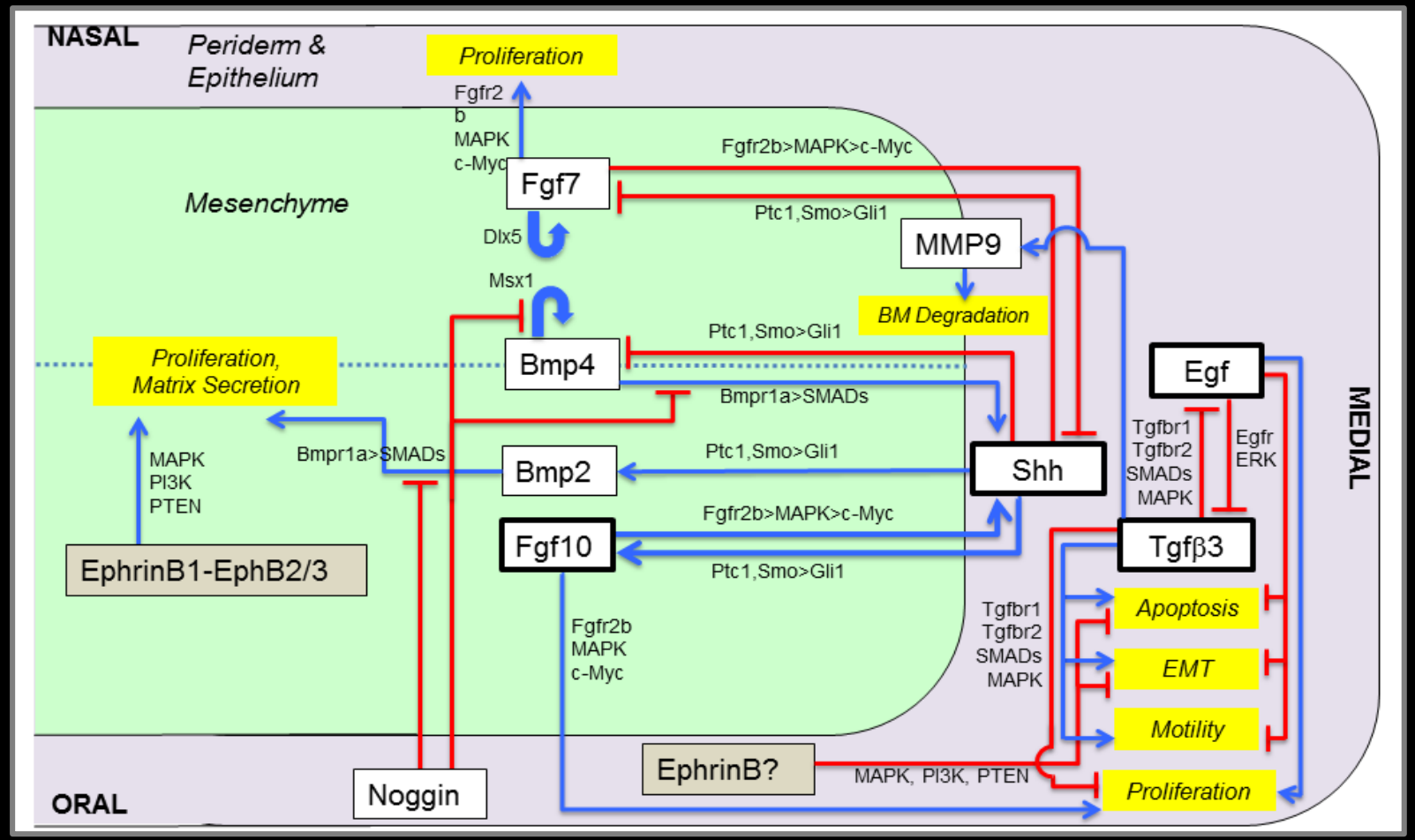
in silico

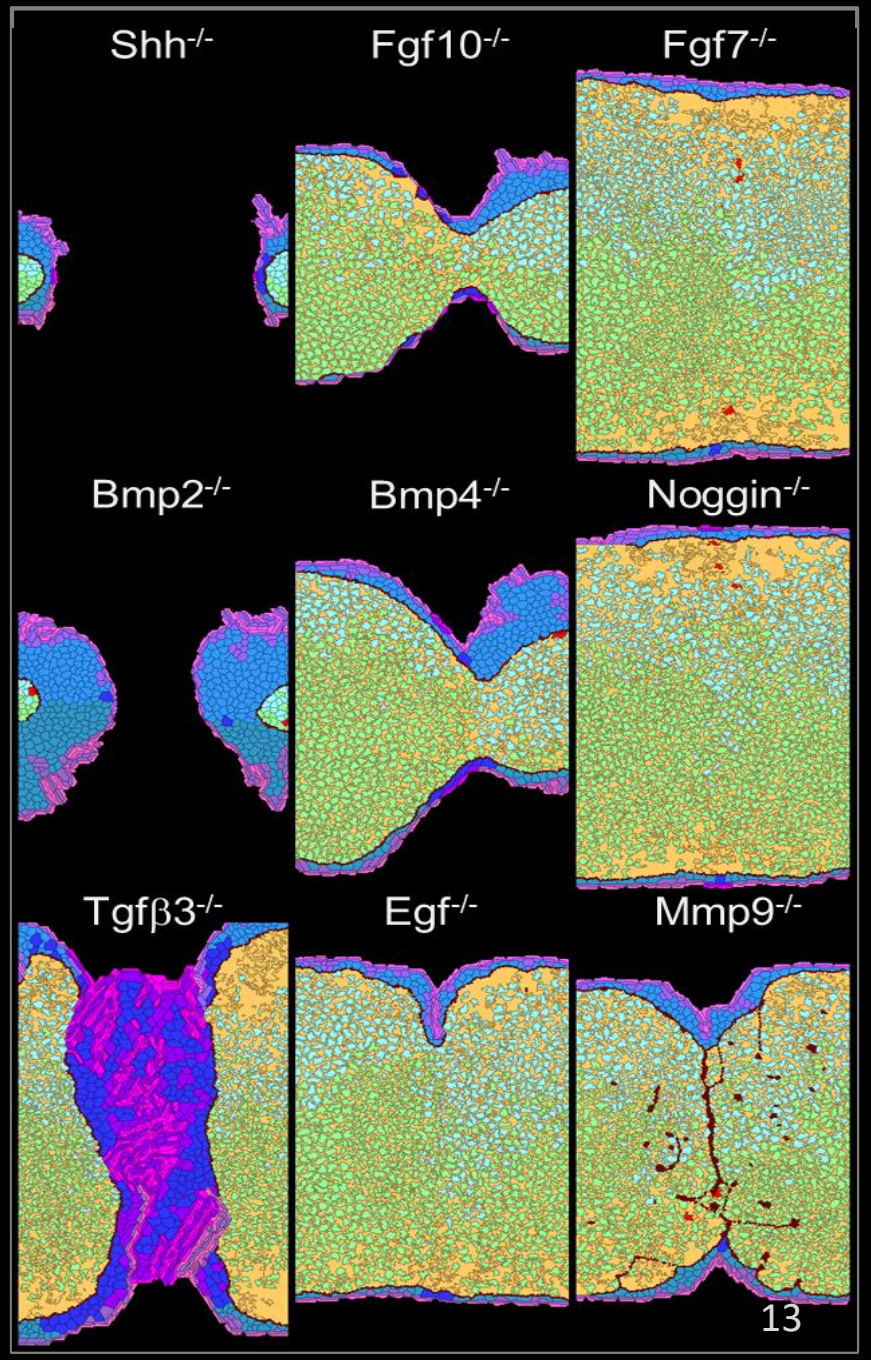




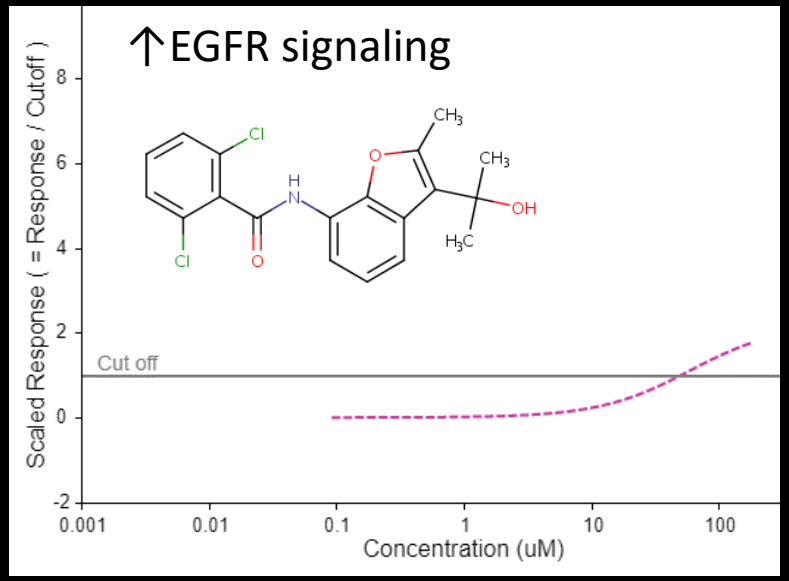
SOURCE: Hutson et al. (2017) Chem Res Toxicol

Hacking the control network → 'Cybermorphs'

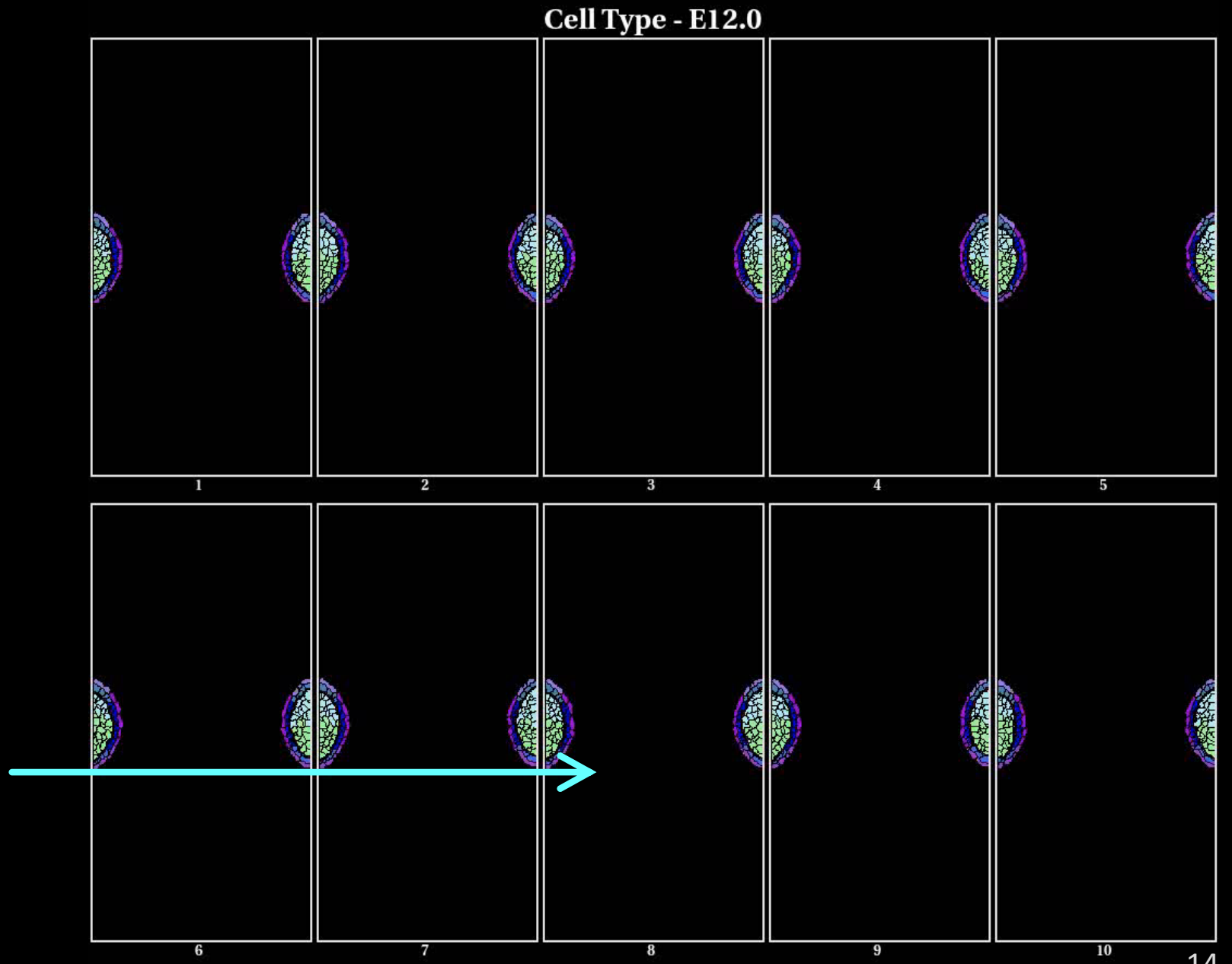




Simulated dose-response



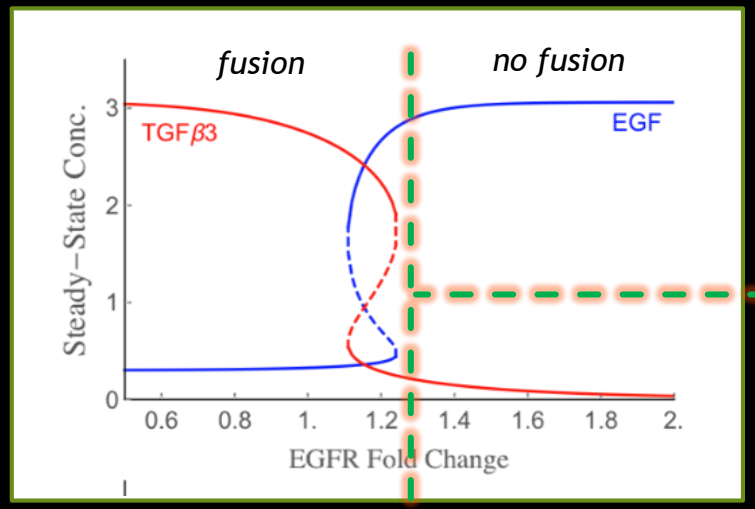
Tipping point predicted in topological context



SOURCE: R Spencer, EMVL

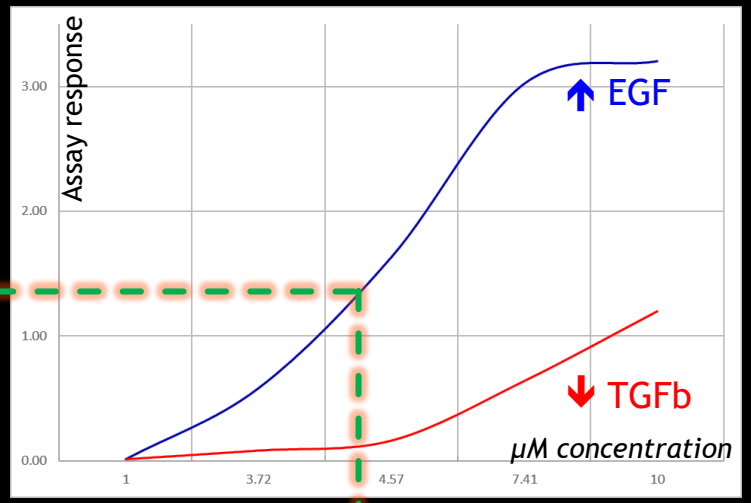
TGF-beta/EGF latch switch: *controls MEE breakdown*

INPUT: switch dynamics



tipping point predicted by computational dynamics (hysteresis switch)

Captan in ToxCast

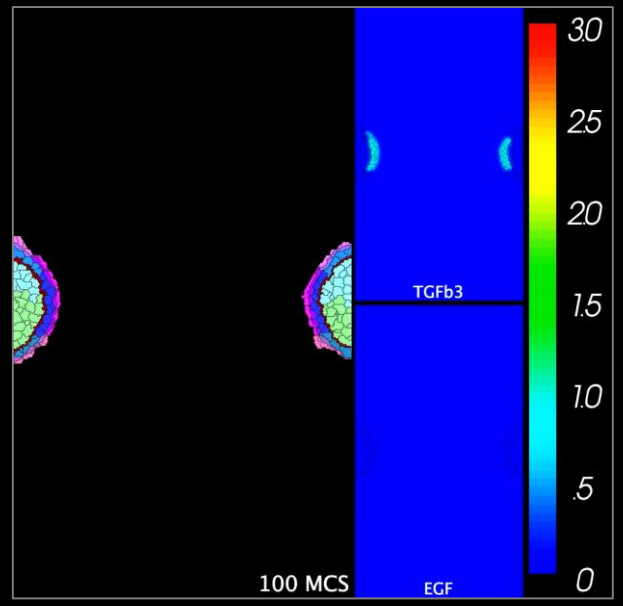


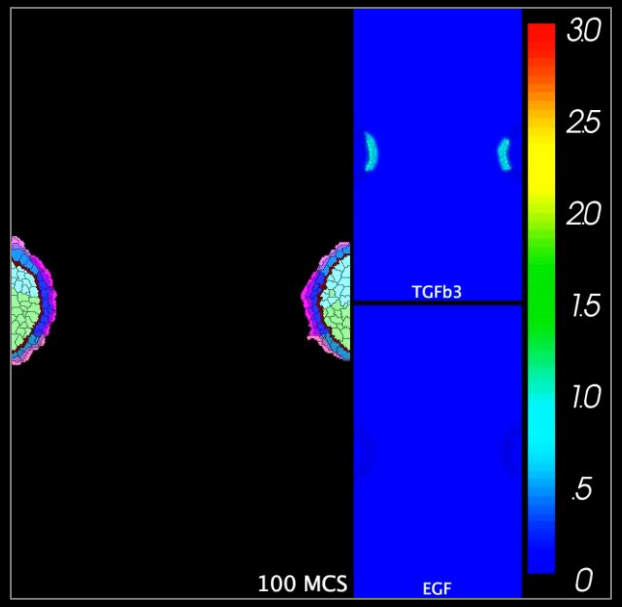
OUTPUT: tipping point mapped to concentration response (4 μM)

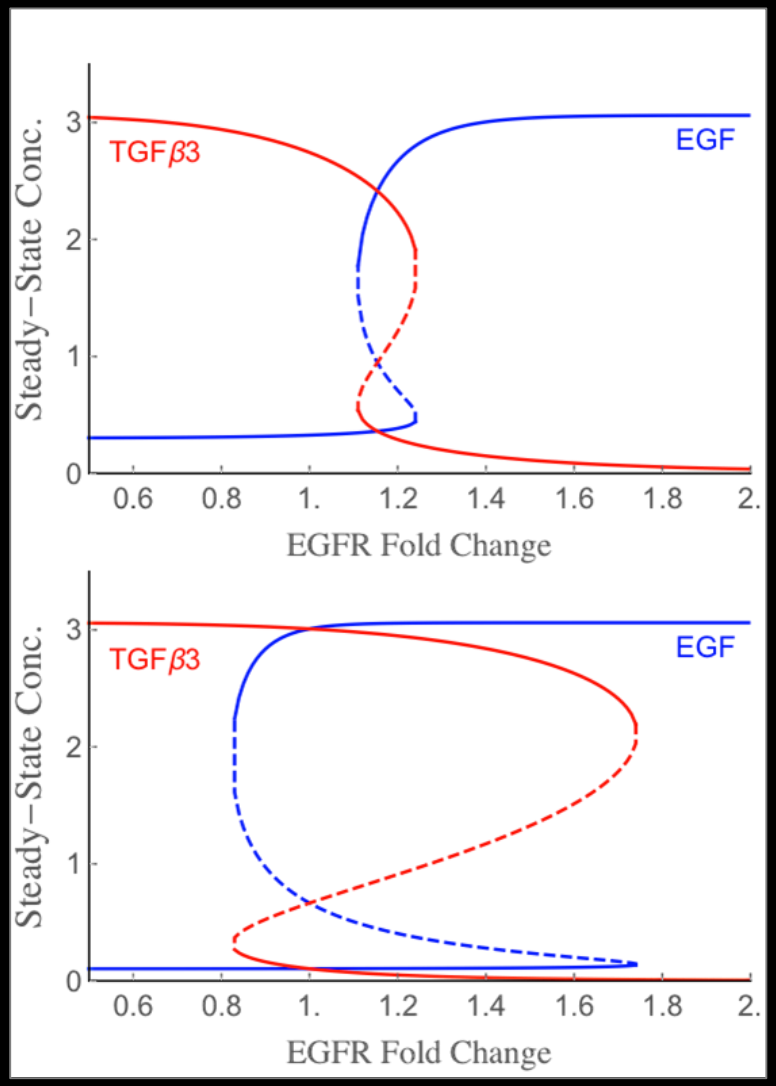
Captan in ToxRefDB
NOAEL = 10 mg/kg/day
LOAEL = 30 mg/kg/day

human HTTK model
2.39 mg/kg/day would achieve a steady state of 4 μM in fetal plasma

Messin' with the switch: *two scenarios for bistable dynamics*





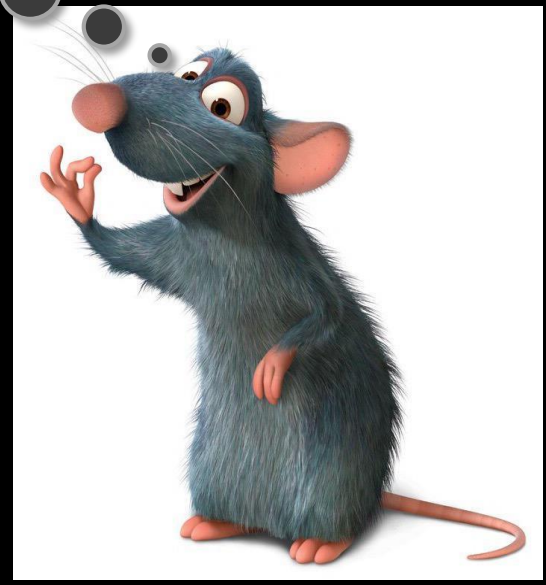


Narrow hysteresis: *less resilient but reversible*

Broad hysteresis: *more resilient but irreversible*

Agent-Based Models (ABMs):

Multicellular simulation is 3R's compliant!



- reconstruct priority systems of embryonic development cell-by-cell and interaction-by-interaction (*emergence*)
- execute tissue simulations that advance through critical determinants of phenotype (*self-organizing phenotypes*)
- simulate *in vitro* data under various *in vivo* scenarios - dose or stage response, critical pathways, non-chemical stressors, etc (*dynamics*)
- probabilistic rendering of where, when and how a defect might occur under different exposure scenarios (*mechanistic interpretation*)

Special Thanks

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- James Glazier – Indiana U
- Sid Hunter – NHEERL / ISTD
- Kyle Grode – NHEERL (now Nikon)
- Andrew Schwab – NHEERL/ISTD
- Barbara Abbott – NHEERL/TAD
- Imran Shah - NCCT
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- Shane Hutson – Vanderbilt U (VPROMPT)
- Bill Murphy – U Wisconsin (HMAPS)
- Bill Daly – U Wisconsin (HMAPS)
- Eric Nguyen – U Wisconsin (HMAPS)
- Guarav Kauschik – U Wisconsin (HMAPS)
- Brian Johnson – U Wisconsin
- Aldert Piersma – RIVM, The Netherlands
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- Nisha Sipes – NCCT (now NTP)
- George Daston – Procter & Gamble Co.

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