Computational Modeling of Developmental Toxicity

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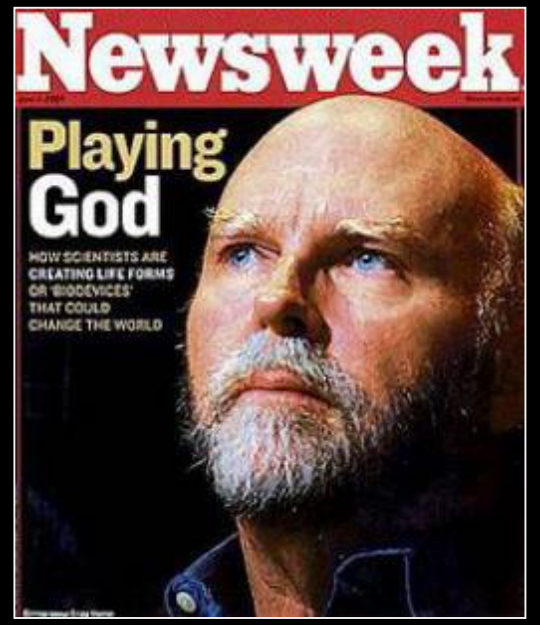
DISCLAIMER: The views expressed are those of the presenter and do not necessarily reflect Agency policy.

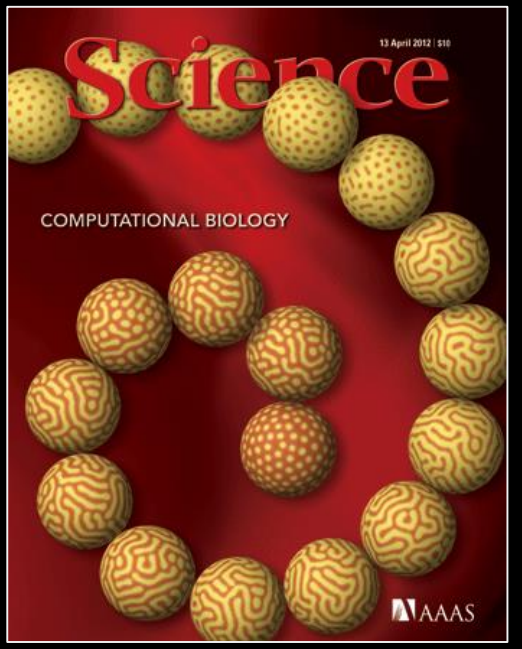
Computational Biology

- On design and fabrication of a minimal cell: *“This is the first self-replicating species we have had on the planet whose parent is a computer.”* -- Craig Venter, 2010

- On graduate training: “If I were a senior or first-year graduate student interested in biology, I would migrate as fast as I could into the field of computational biology." -- Francis Collins, 2012

- On the problems best-suited to computational biologists: “… finding useful signals in tremendously large sets of unsorted, noisy data.” -- Russ Altman, 2012





In a nutshell …

- Advances in biomedical, engineering, and computational sciences enable high-throughput screening (HTS) to profile the toxicological landscape (*ToxCast/Tox21*).
- Surfeit of HTS data and information now in hand, practical need arises to tie these data in some way to formal biological understanding of toxicity (*MOAs, AOPs*).
- Information must be collected, organized, and assimilated into computer models (*in silico*) that link HTS data (*in vitro*) to apical outcome *(in vivo)* (*predictive toxicology*).
- Computational biology is uniquely position to capture this connectivity and help shift decision-making to mechanistic pathways (*systems models*).

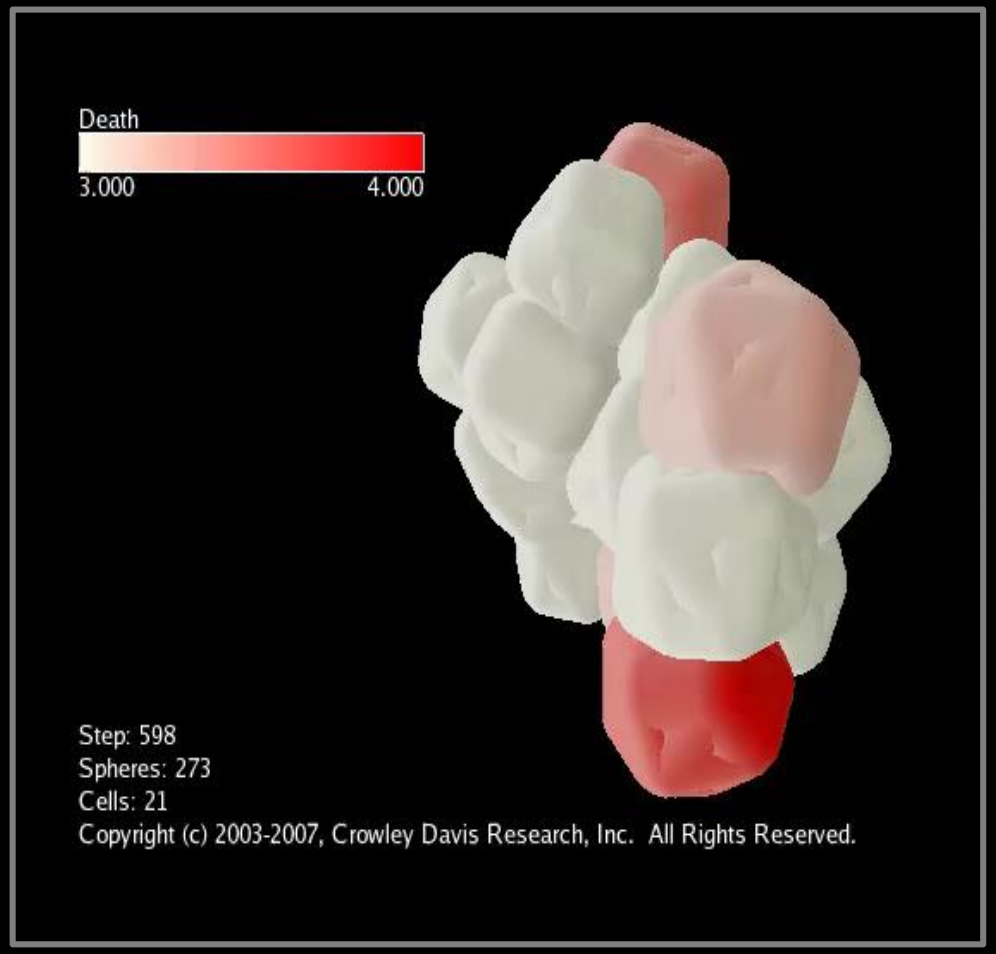
… this is not so easy!

- **Biological systems are complex:** networks of ‘nodes’ (molecules) and ‘edges’ (interactions) operate in nonlinear fashion across space and time to control cellular fate and behavior:
  - cell growth, proliferation, adhesion, differentiation, polarization, motility, apoptosis, …

- **Systems are wired for robustness:** cross-talk in cell signaling may dampen how a multicellular system reacts to microphysiological perturbations:
  - how does cellular injury alter developmental dynamics?

- **Agent-Based Models (ABMs):** formal approach to explain/predict how changes in a complex dynamical system propagate to a critical effect (eg, malformation).
  - the biological unit (cell) is taken as the computational unit (agent) in a dynamical simulation.

Anatomical homeostasis in a self-regulating Virtual Embryo



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

Building and testing agent-based models models (ABMs) for predictive DART:

- *reconstruct tissue development cell-by-cell, interaction-by-interaction*
- *pathogenesis following synthetic knockdown (cybermorphs)*
- *introduce ToxCast lesions into a computer simulation*
- *return quantitative predictions of where, when and how the defect arises.*

Case Studies for Predictive Toxicology in a 'virtual embryo'

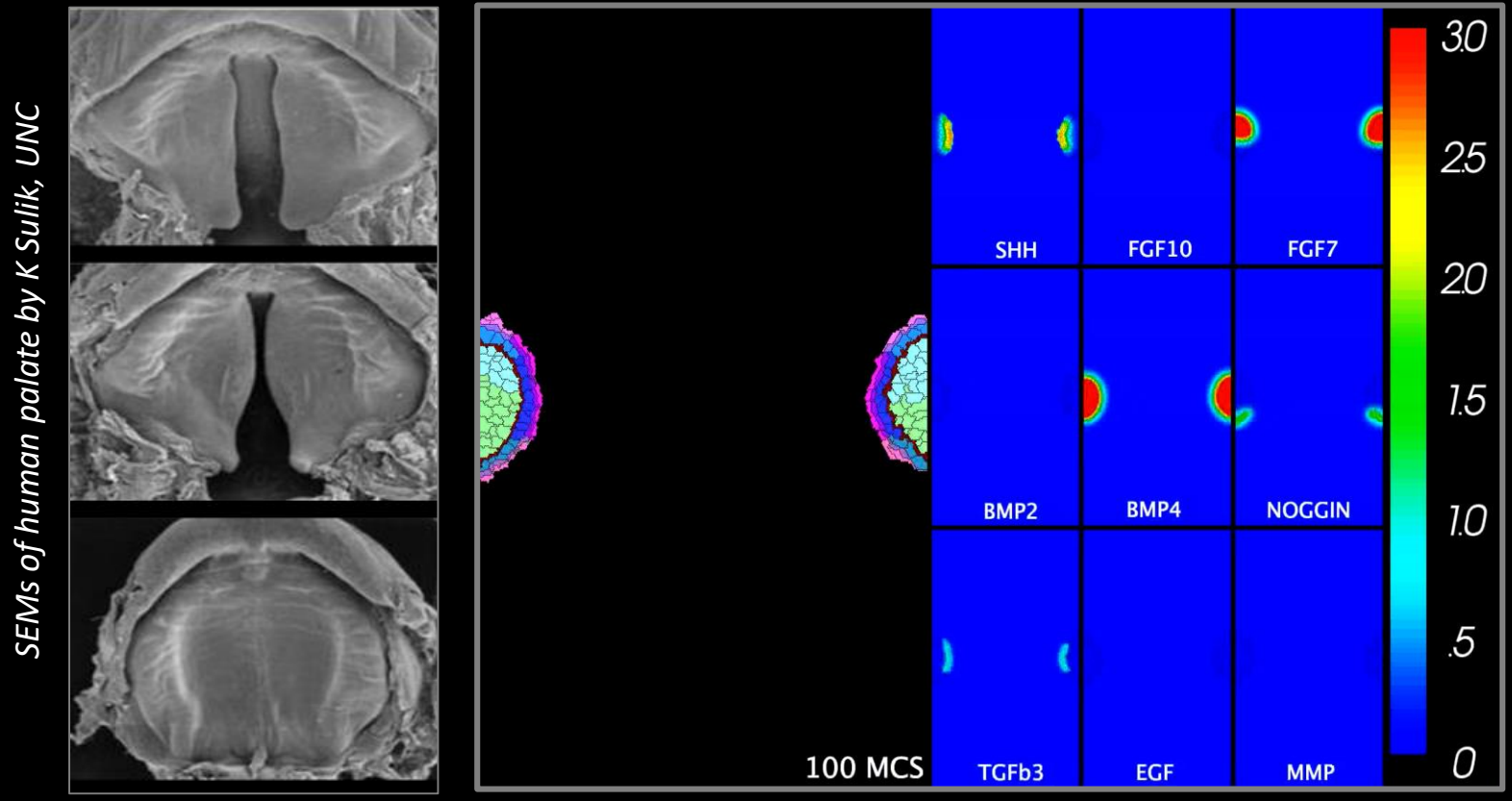
CASE 1: Reverse-engineering the system: *suppose we know an apical outcome (eg, malformation), how far can an ABM take us to inferring a key event quantitatively?*

CASE 2: Forward engineering the system: *suppose we know a molecular effect (eg, ToxCast lesion), how far can an ABM take us to hypothesizing an apical outcome?*

1. Reverse-engineering the system: *top-down scaling*

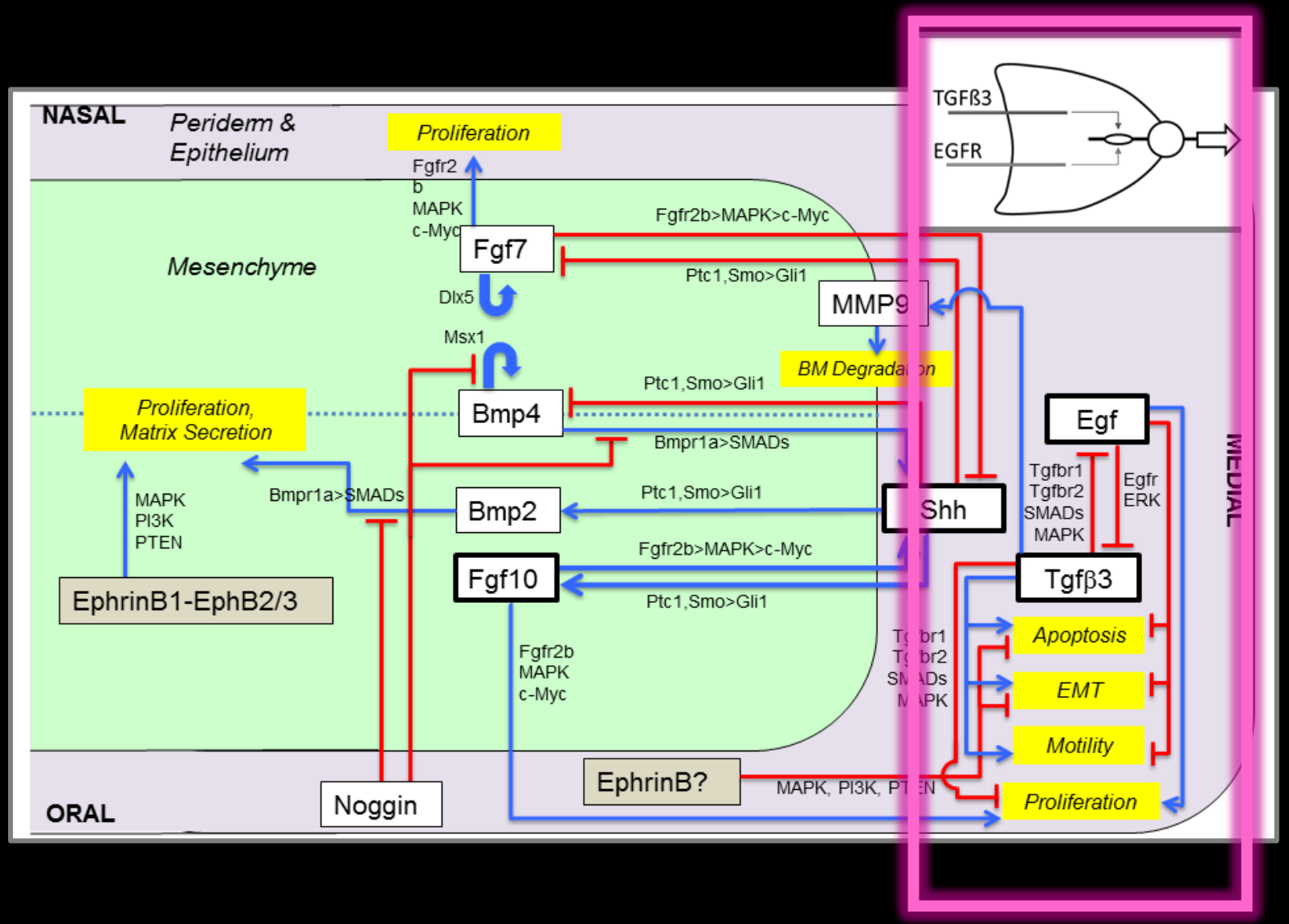
Palatal fusion *in vivo*

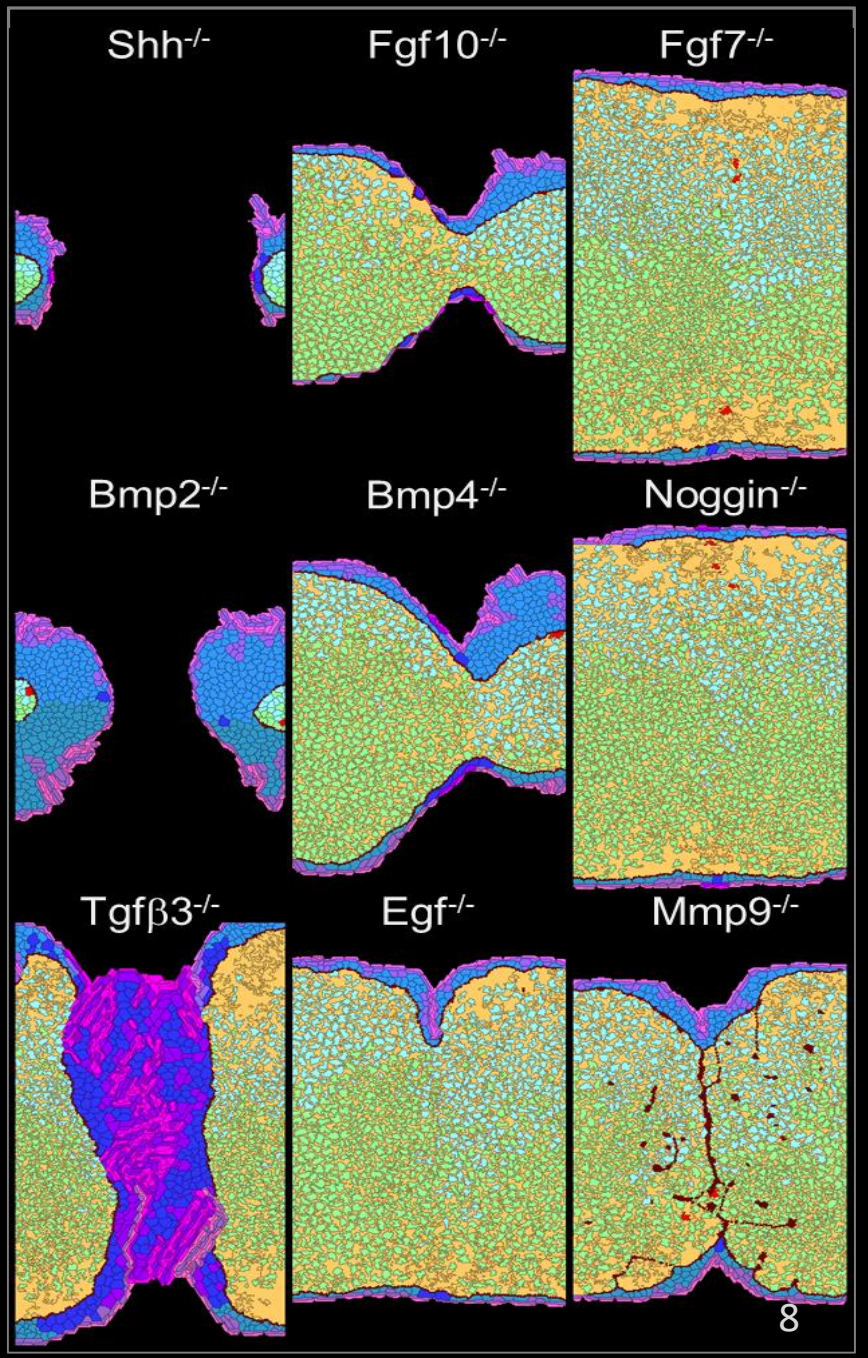
Palatal fusion *in silico*



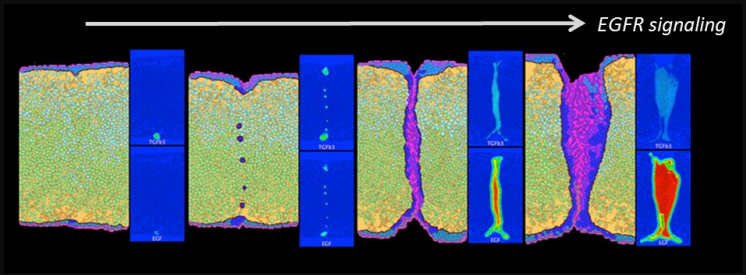
Hutson et al. (2017) Chem Res Toxicol

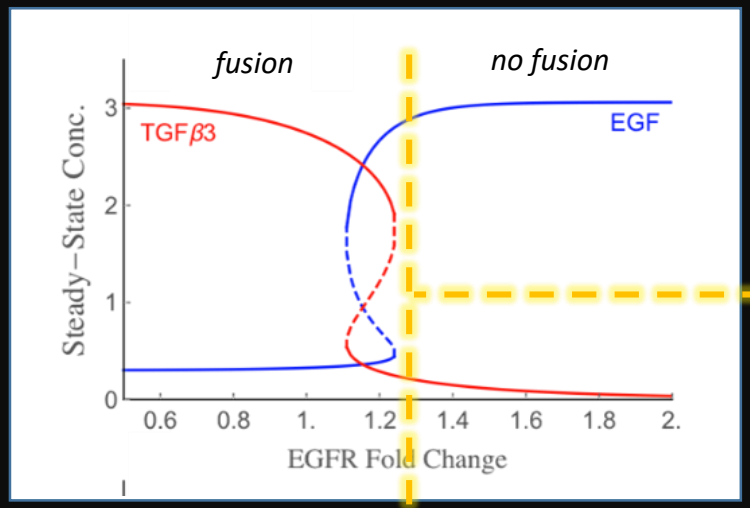
Hacking the control network → 'Cybermorphs'





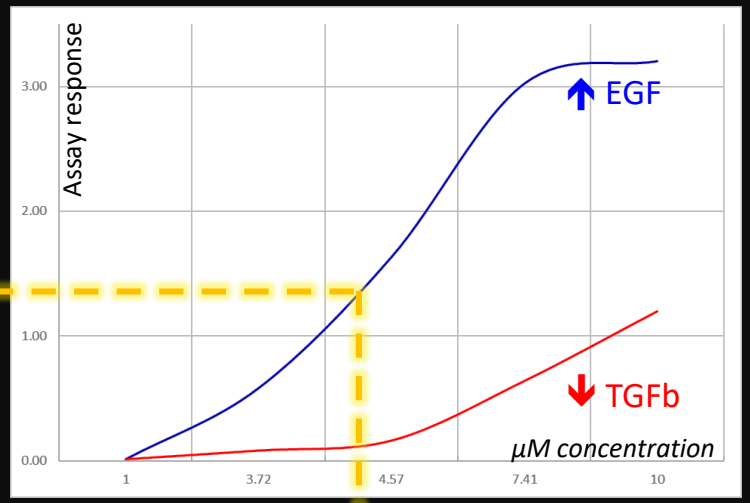
Cybermorph → ToxCast lesion: Captan-induced cleft palate in rabbits





OUTPUT: tipping point predicted by computational dynamics (hysteresis switch)

INPUT: Captan in ToxCast



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

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

HTTK pregnancy model predicts **2.39 mg/kg/day** Captan would achieve a steady state concentration of 4 µM in the fetal plasma

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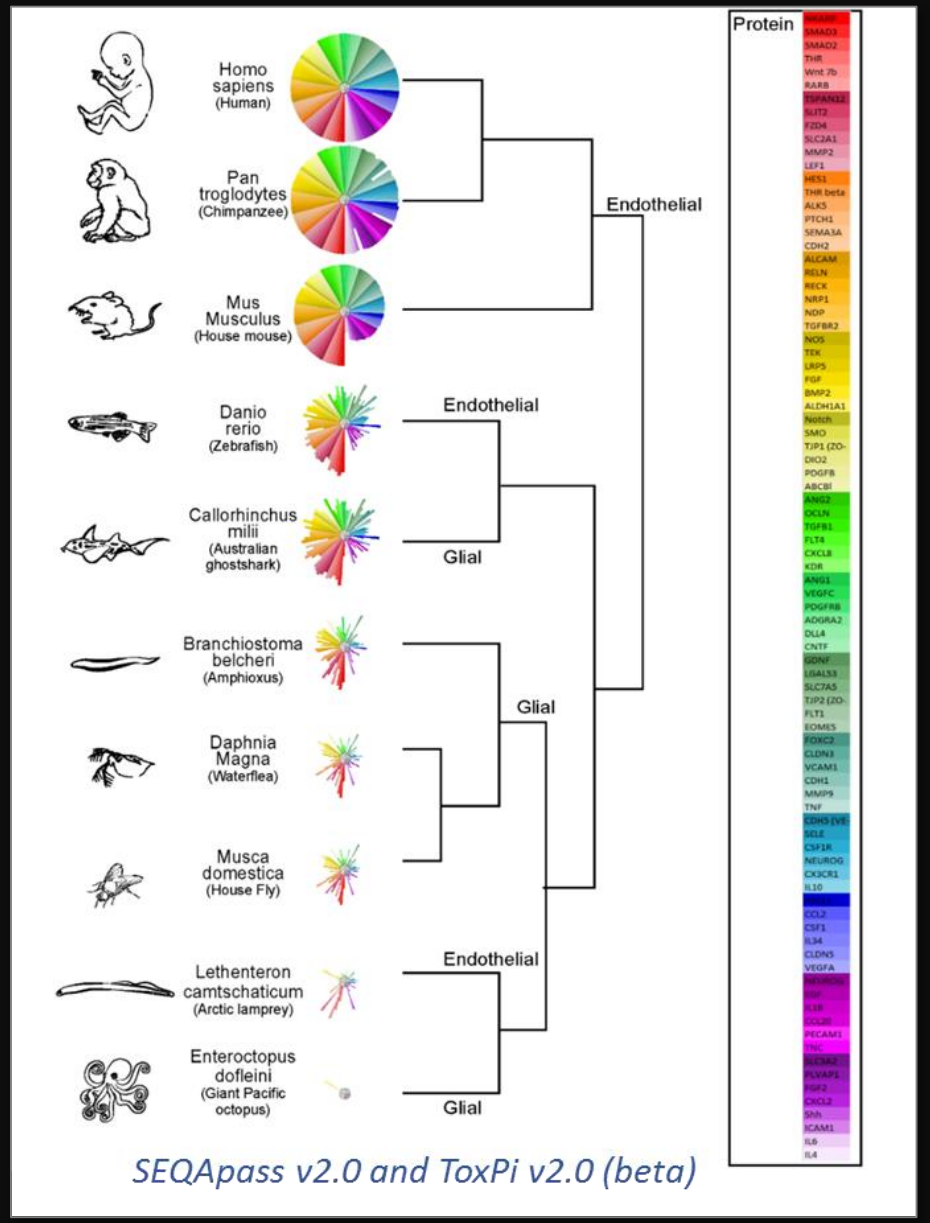
2. Reverse-engineering the system: *bottom-up scaling*

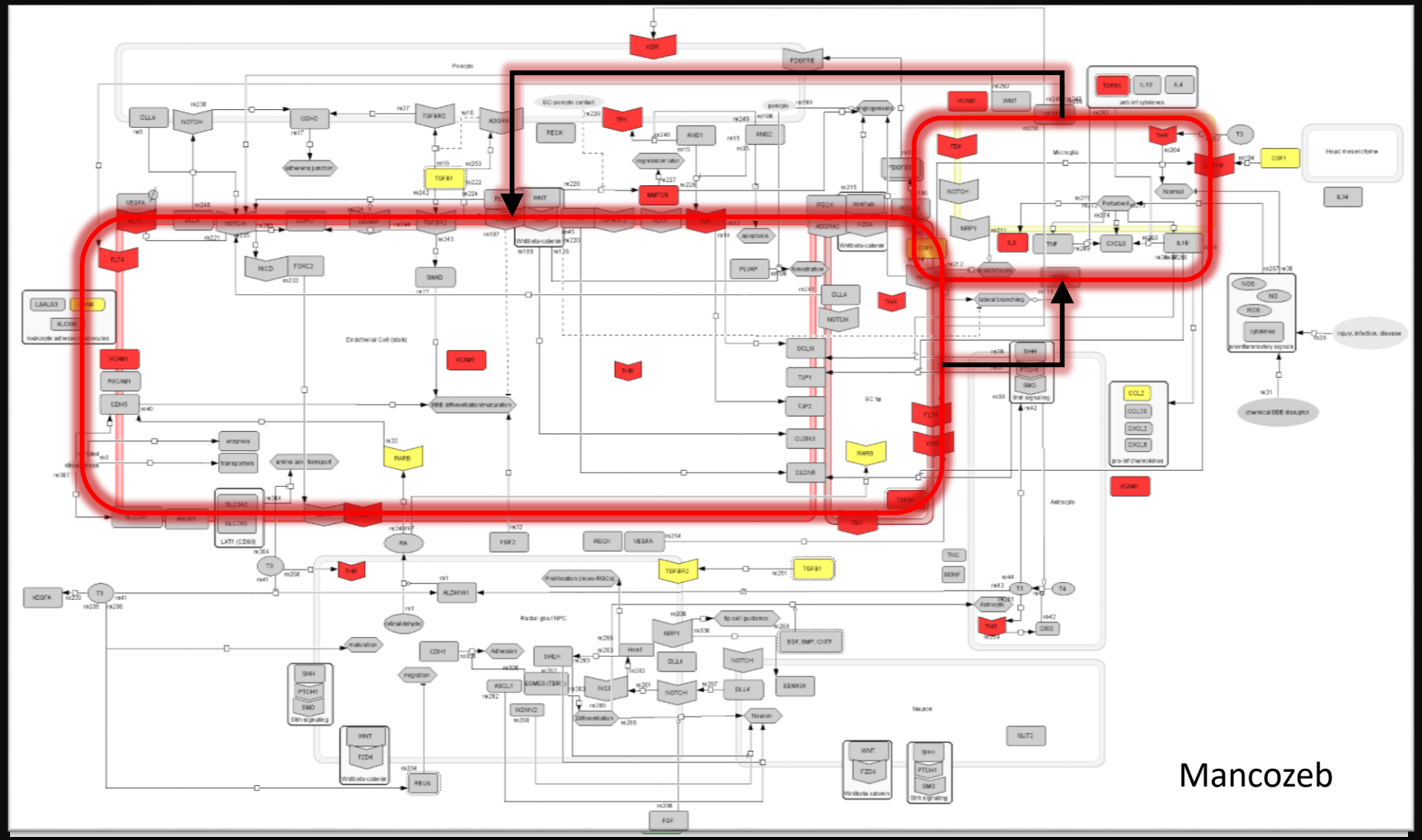
Blood-Brain Barrier (BBB):

- Functional interface developing between vascular (and neural compartments of the CNS.
- System evolves in molecular complexity - mining the literature landscape identified >90 genes, >5 cell types.
- Archeotypical pathways – Glut1, SHH, Notch-DLL … advanced pathways – neuro/angiogenic signals.



Saili et al. (2017) manuscript under internal review

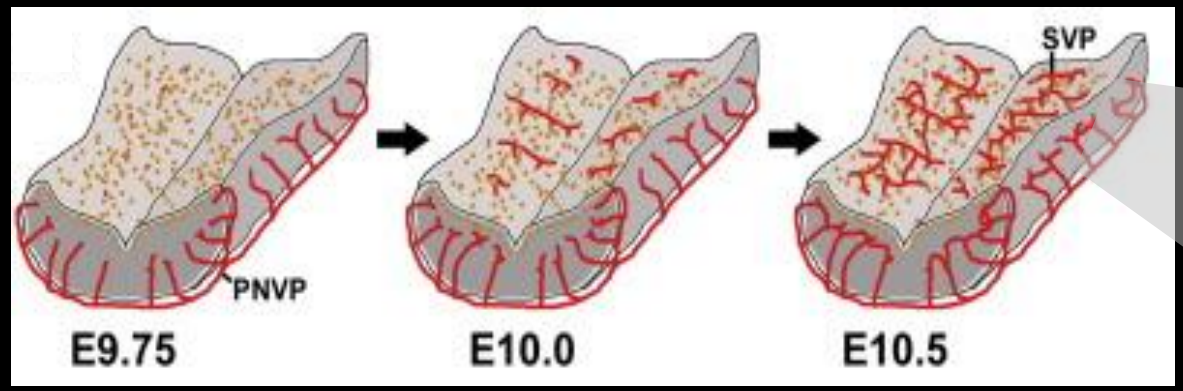
BBB ontogeny: *blueprint of cellular interactions*



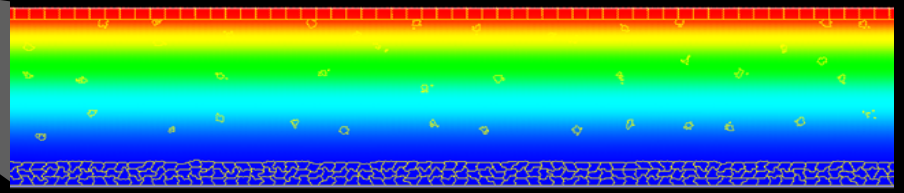
Saili et al. (2017) manuscript under internal review

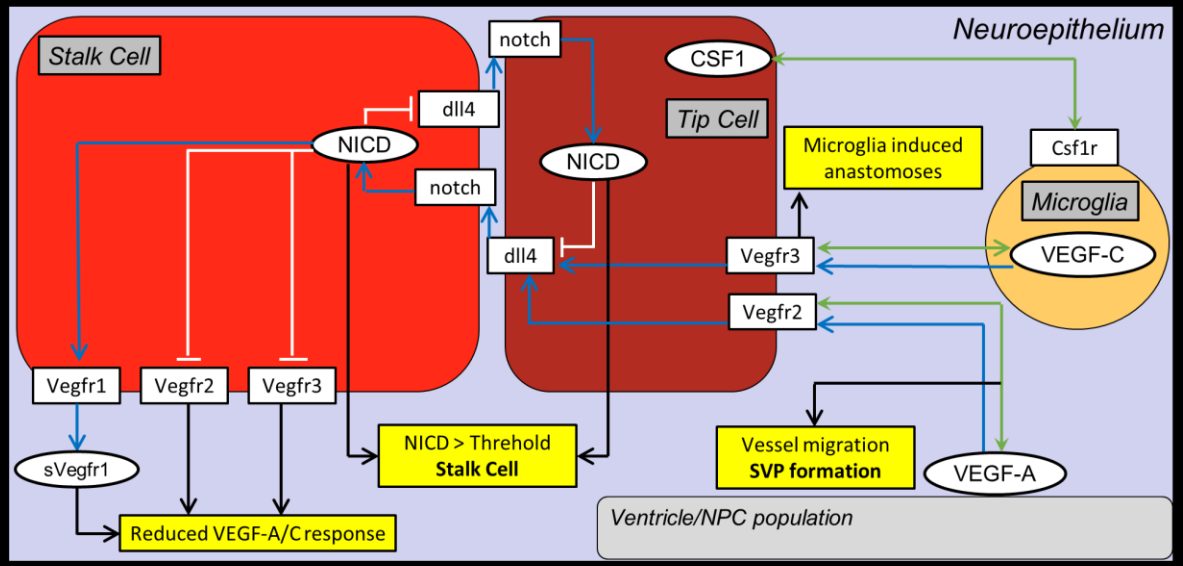
Modeling Brain Angiogenesis: *cellular agent-based model of arborization*

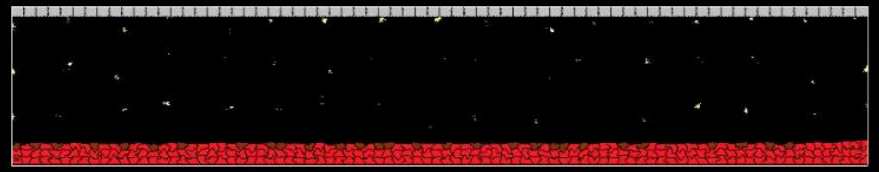
Tata et al. (2015) *Mechanism Devel*



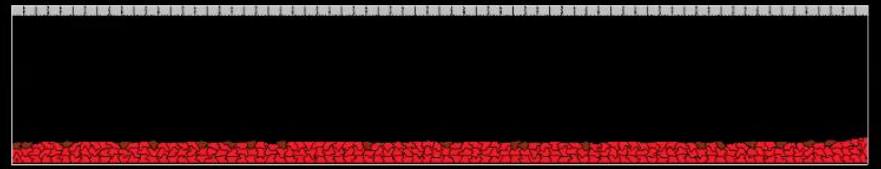
VEGF-A gradient: NPCs in subventricular zone

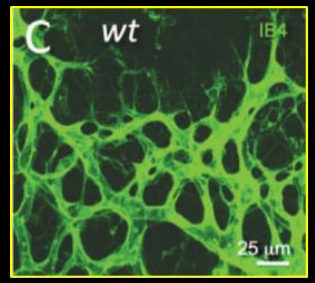


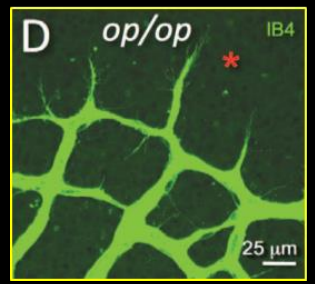




endothelial tip cell
endothelial stalk cell
microglial cell





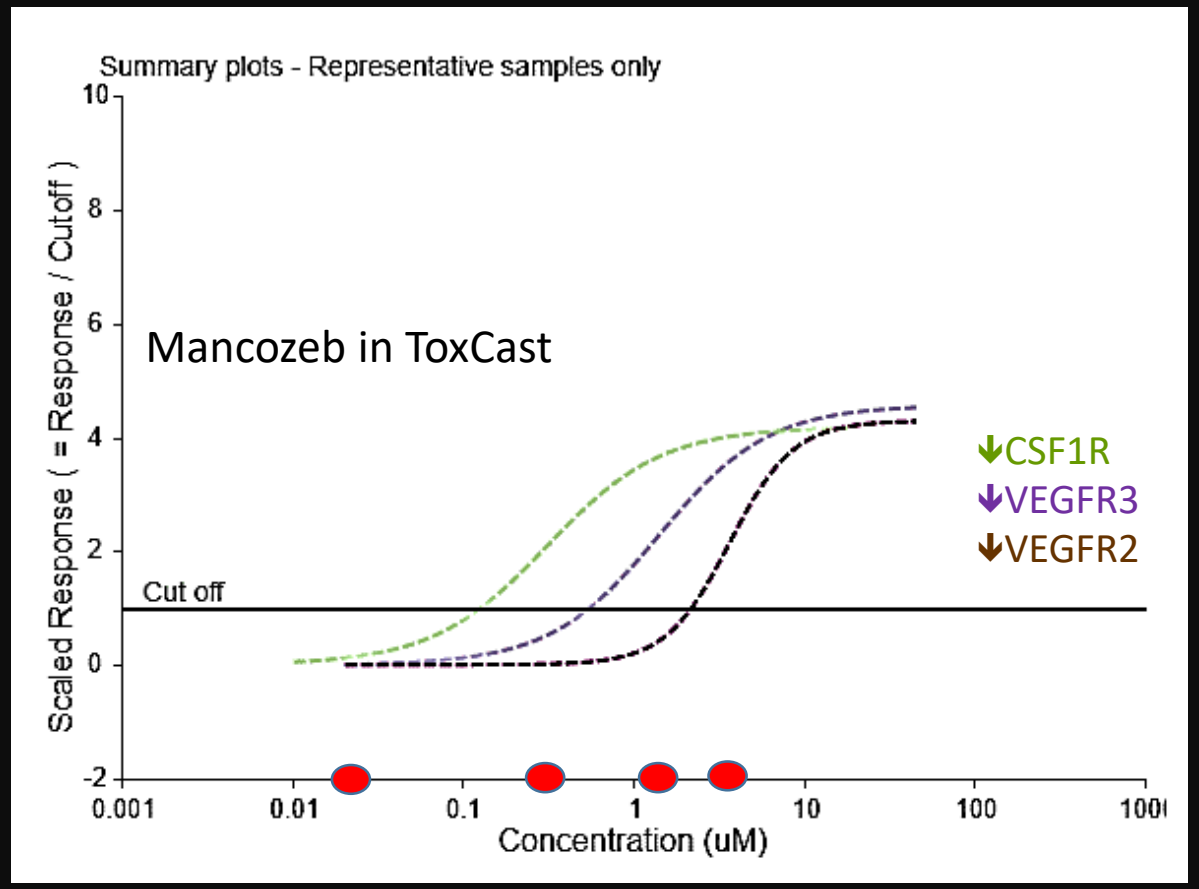


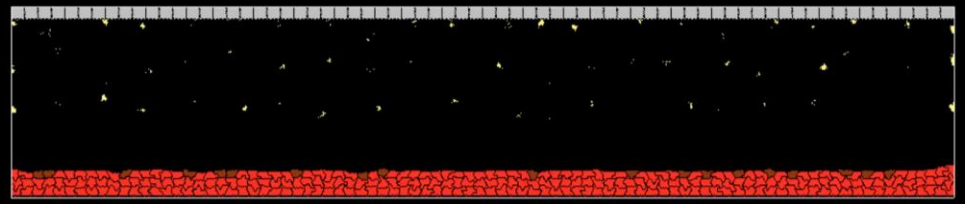
Rymo et al. (2011) PLoS one

SOURCE: T Zurlinden – NCCT (2017)

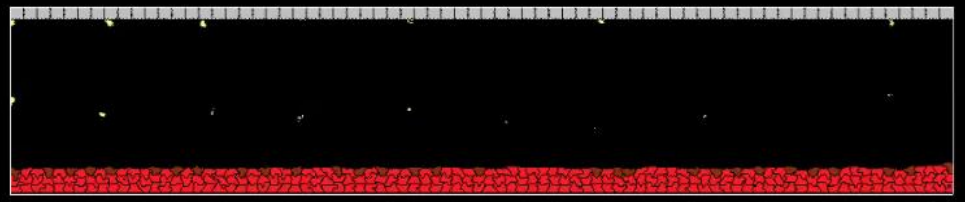
In silico cascading dose scenario

endothelial tip cell
endothelial stalk cell
microglial cell

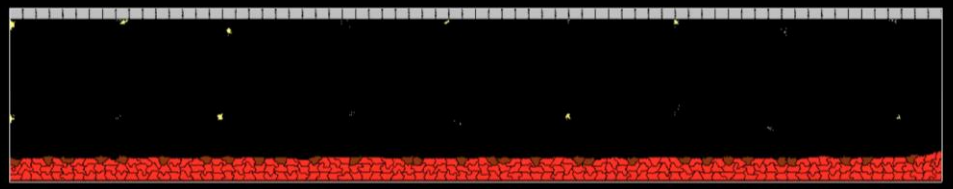




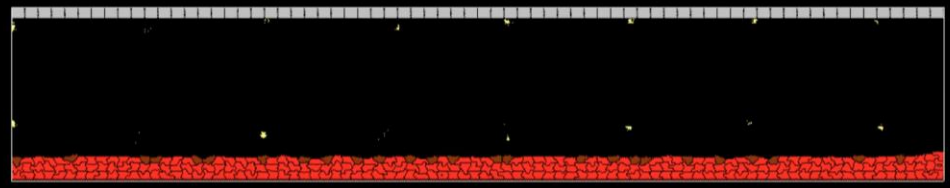
INPUT 0.03 µM
OUTPUT: predicted dNEL



INPUT 0.3 µM: AC50 CSF1R
OUTPUT: fewer microglia drawn to EC-tip cells



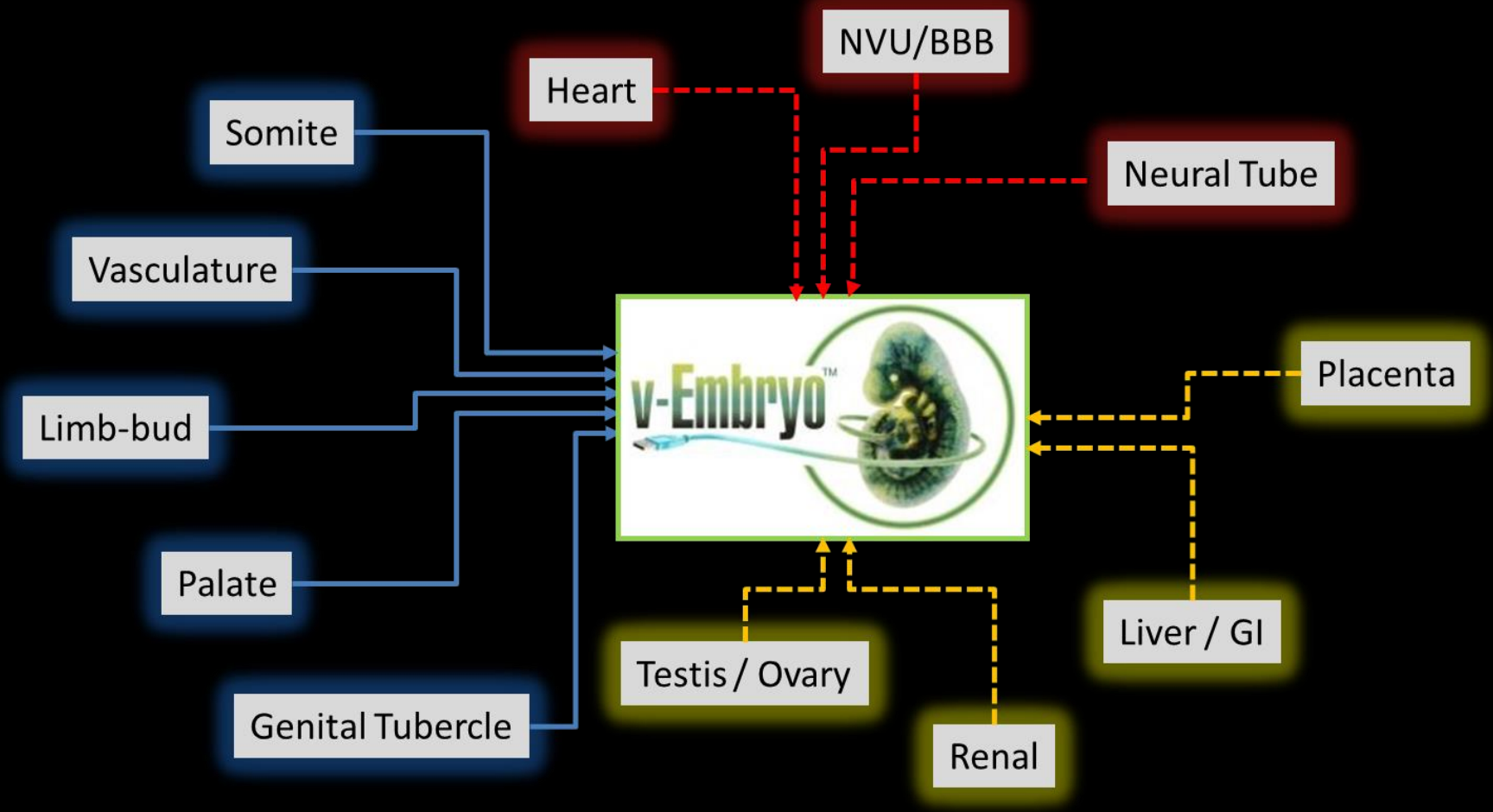
INPUT 2.0 µM: AC80 CSF1R + AC50 VEGFR3
OUTPUT: overgrowth of EC-stalk cells



INPUT 6.0 µM: AC95 CSF1R + AC85 VEGFR3 + AC50 VEGFR2
OUTPUT: loss of directional sprouting

Zirlinden et al. (2017) manuscript in preparation

Virtual Embryo: an array of ABMs to forward- and reverse-engineer DevTox.



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