



Complex Systems Science: CSS 17.02

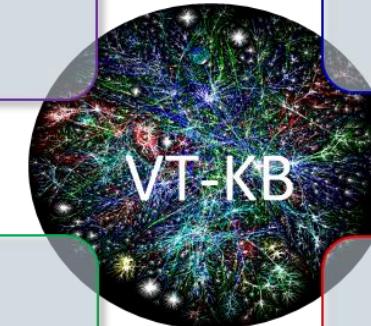
Virtual Tissue Models (VTMs)

Classification
models

Adverse Outcome
Pathways

Biological
information

CompuCell3D
(ABMS)



CSS BOSC - November 16, 2016

Weekly VTM Meetings 10 am – 12 noon, RTP E101

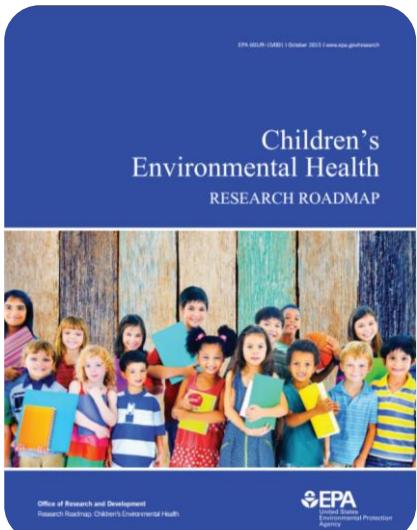
Call-in: 1-866-299-3188 (#9195419776)

Webinar: <https://epawebconferencing.acms.com/vtm/>

[http://vtm.epa.gov/mediawiki/index.php/Main_Page#Welcome to the Virtual Tissue Modeling Wiki](http://vtm.epa.gov/mediawiki/index.php/Main_Page#Welcome_to_the_Virtual_Tissue_Modeling_Wiki)

DISCLAIMER: The views expressed are those of the presenters and do not necessarily reflect the views or policies of the Agency.

Rationale



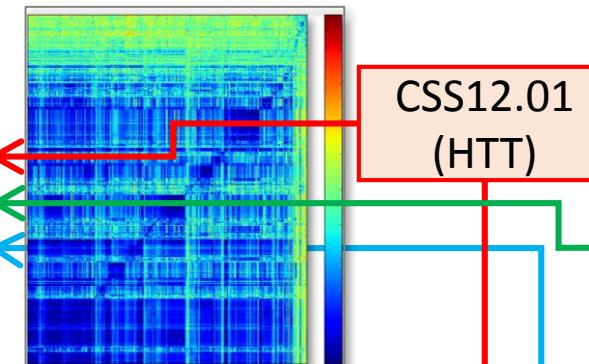
- The question of how tissues are shaped during development is central to embryology and developmental toxicology.
- Individual cell behaviors (mitosis, migration, differentiation, adhesion, apoptosis, ECM remodeling, ...) must be coordinated in time and space.
- ToxCast provides HTS data at the cellular-molecular scale but more complex systems are needed to model morphoregulatory AOPs.
- Virtual Tissue Models (VTMs) aim to fill this gap and improve our ability to predict how chemicals may impact human development.

CSS 17.02 (VTM) products and integration



MORPHOGENESIS

- 17.02.1 - Morphogenetic Fusion
- 17.02.2 - Epithelial-Mesenchymal Transition



THYROTROPIC NEURODEVELOPMENT

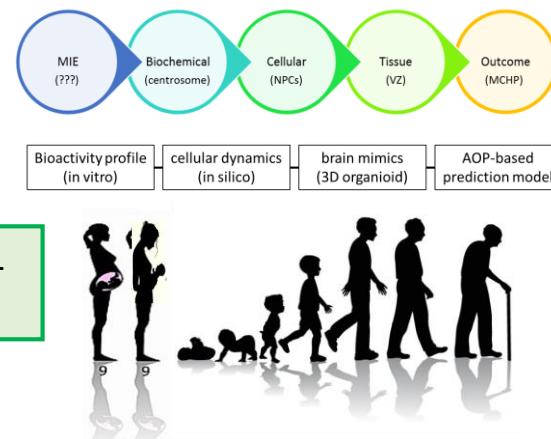
- 17.02.3 - Fetal Physiome (TH kinetics)
- 17.02.4 - Neurovascular Unit (TH dynamics)

TIPPING POINTS

- 17.02.5 - Microdosimetry
- 17.02.6 - State Dynamics

OCM-PT (STAR) Centers

- HMAPs – University of Wisconsin
- VPROMPPT – Vanderbilt/Pittsburgh
- UW-PTC – University of Washington
- CT-AOP – Texas A&M/NCSU

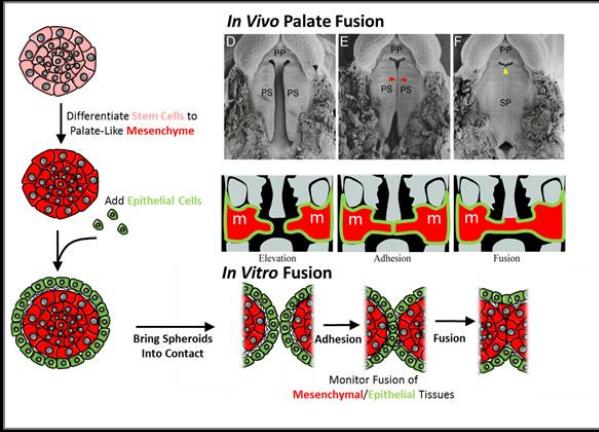


- Integrating *in vitro* data and *in silico* models for predictive toxicology – *spatial dynamics and tissue reconstruction*.
- Complex systems models for developmental toxicity - EPA's *Children's Environmental Health (CEH) Research Roadmap*.
- Engineering microscale tissues & microphysiological systems - *3D OCMs for predictive toxicology STAR Centers*.

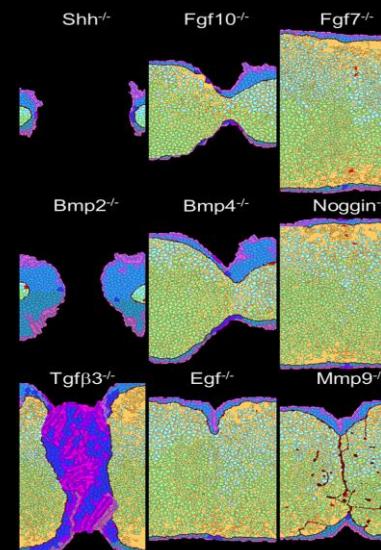
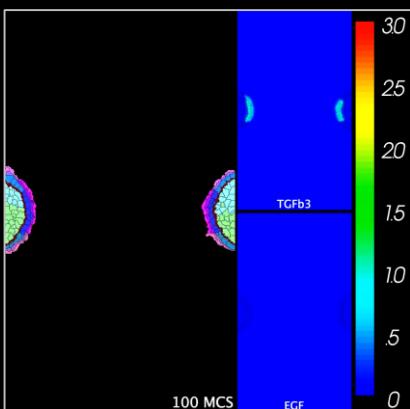
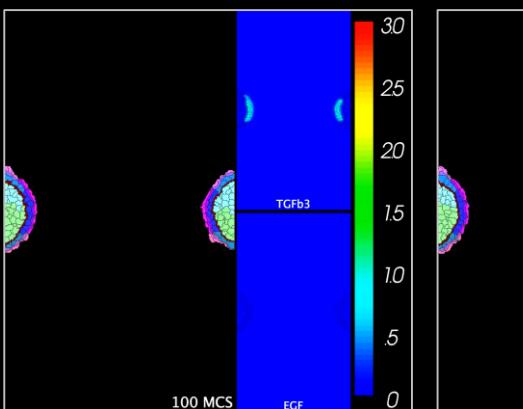


Morphogenetic fusion: a critical embryological process; delay or disruption underlies some common birth defects (eg, cleft palate, hypospadias, spina bifida).

in vitro (human cell-based construct)



in silico (cell agent-based model)



VTM WORKFLOW

bioactivity profiles



biological circuits



cellular dynamics



ABMS 'cybermorphs'



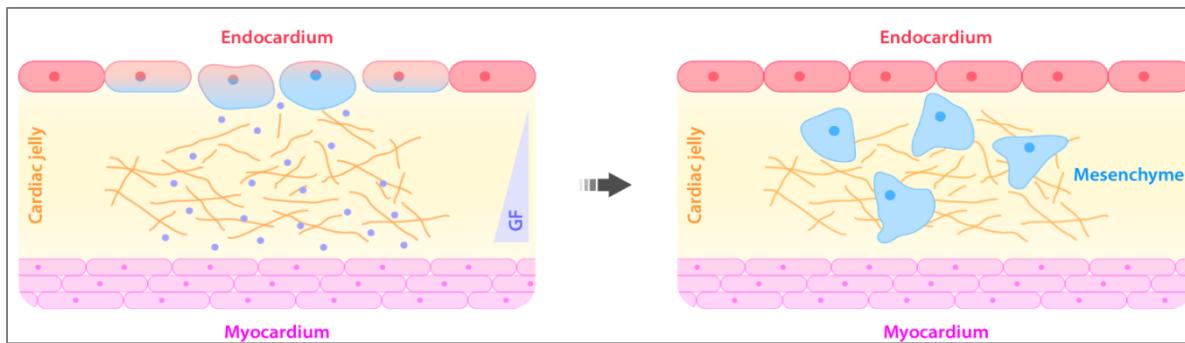
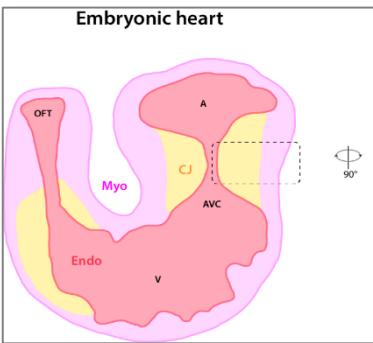
organotypic cultures



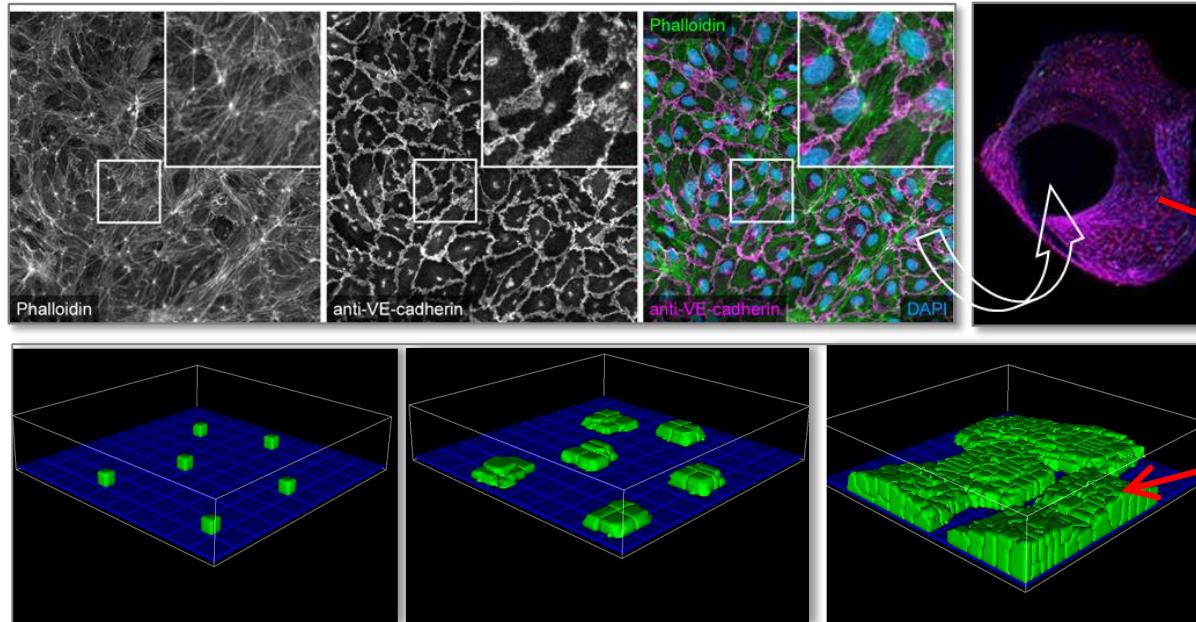
functional analysis

Epithelial-Mesenchymal Transition: a critical embryological process; delay or disruption underlies some congenital malformations (e.g., valvulo-septal heart defects).

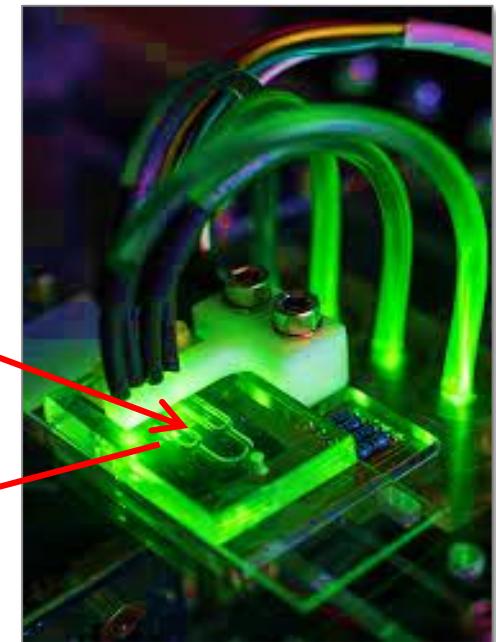
EMT is critical for endocardial cushion development ...



TGF-beta
Wnt
FGF
Chemokine/Cytokine
Integrin
Angiogenesis
Cadherin
GPCR
Notch
PDGF



... but endocardial EMT does not occur in a static environment; need to "go with the flow".

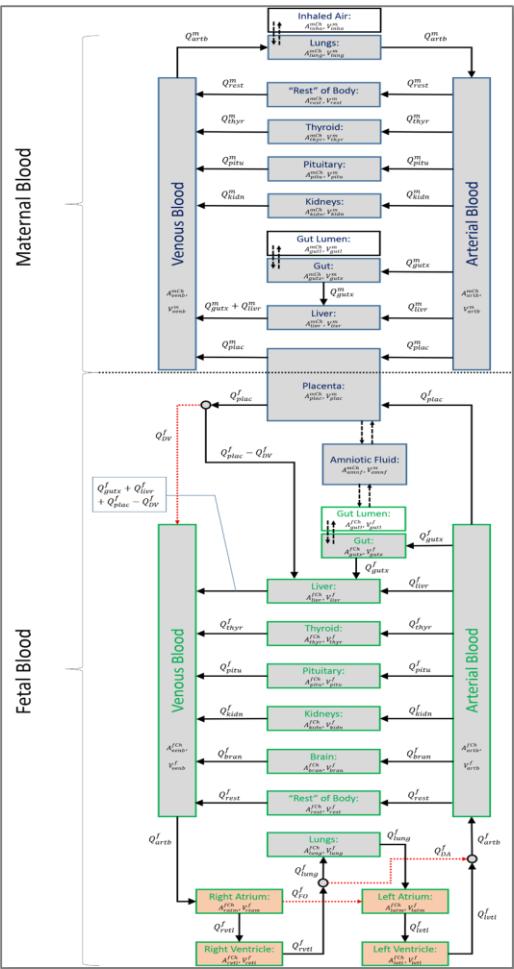


CompuCell3D model to probe microdosimetry (chemicals, signals) in a microphysiological environment of the human embryonic heart.

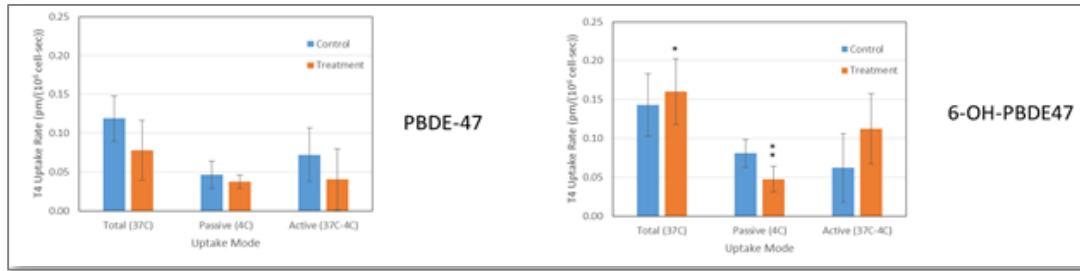
POSTERS 15 & 17

Human Physiome Model: comprehensive HTTK model to predict the impact of thyroid disrupters on thyroid hormone homeostasis during pregnancy-lactation.

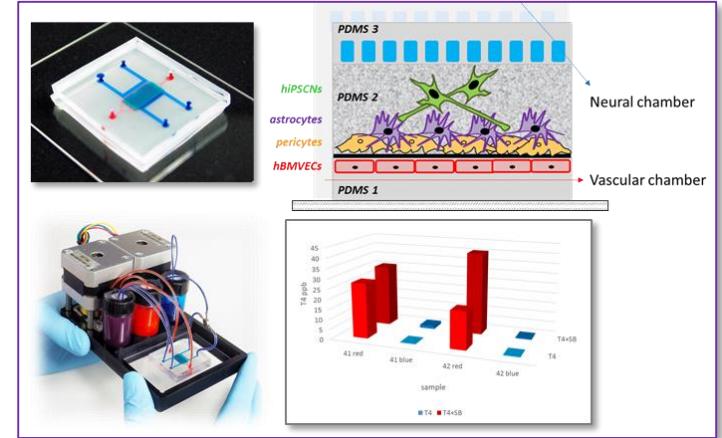
Fetal HTTK model



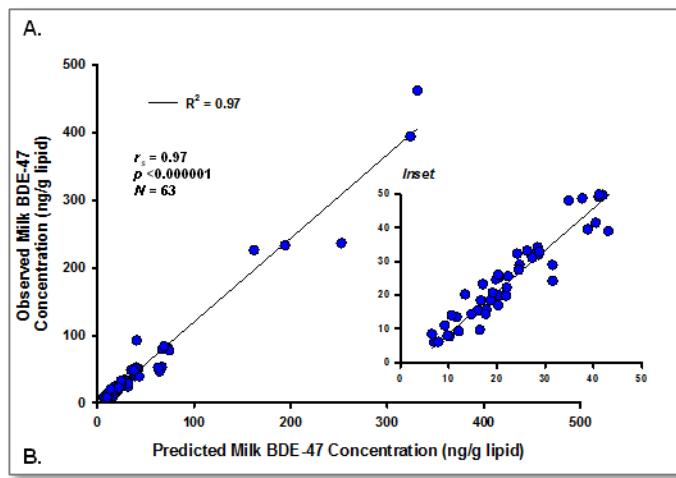
TH transporter kinetics and metabolism (hepatocytes in culture)



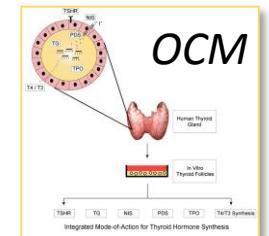
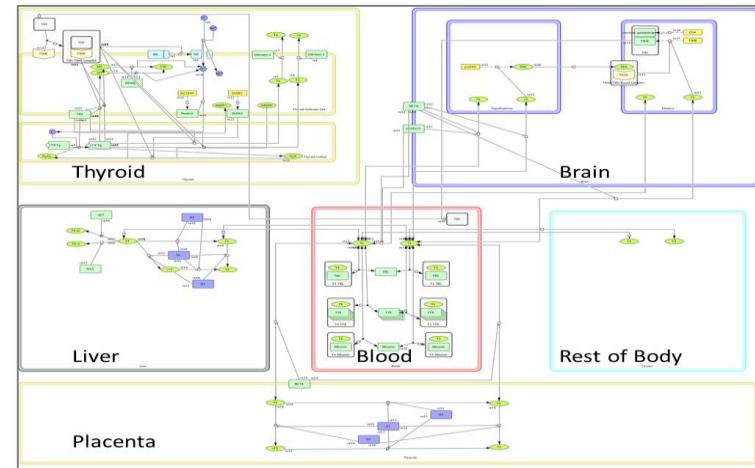
T4 transport dynamics (Vanderbilt's hNVU on a chip)



Neonatal Exposure Model (predicted lactationally)



Tellurium Systems Model



Future:
Homunculus

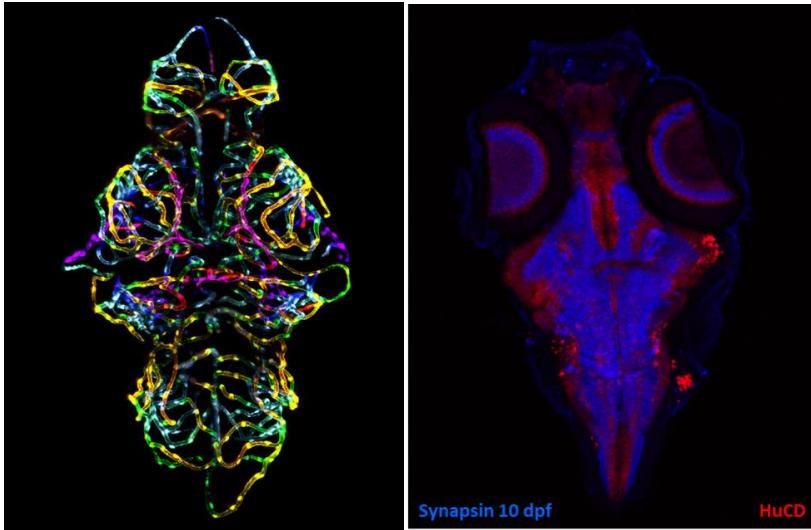
POSTER 12

Neurovascular Unit (NVU): modeling the logistical dynamics of developmental toxicity at the blood-brain barrier and consequences to neuroprogenitor growth.

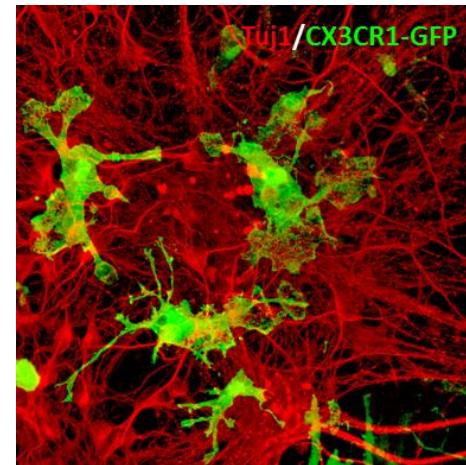
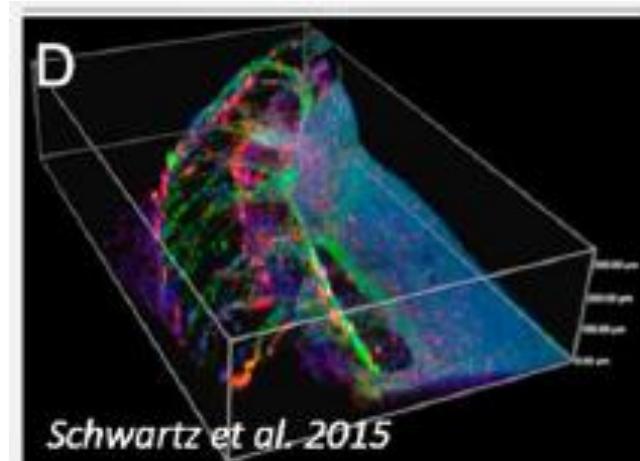
Zebrafish Embryo – molecular dissection

BBB: Source - J Peters, M Taylor – St.Judes

Neural Compartment: T Tal, S Padilla, K Jensen - NHEERL

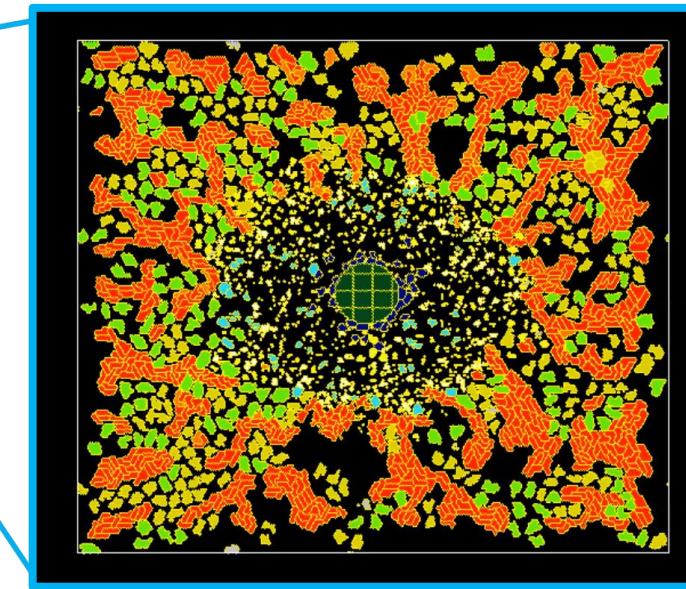


Human Brain Mimics
(HMAPs STAR Center)



Microglia sensing
(A*STAR)

Computational NVU (cNVU)



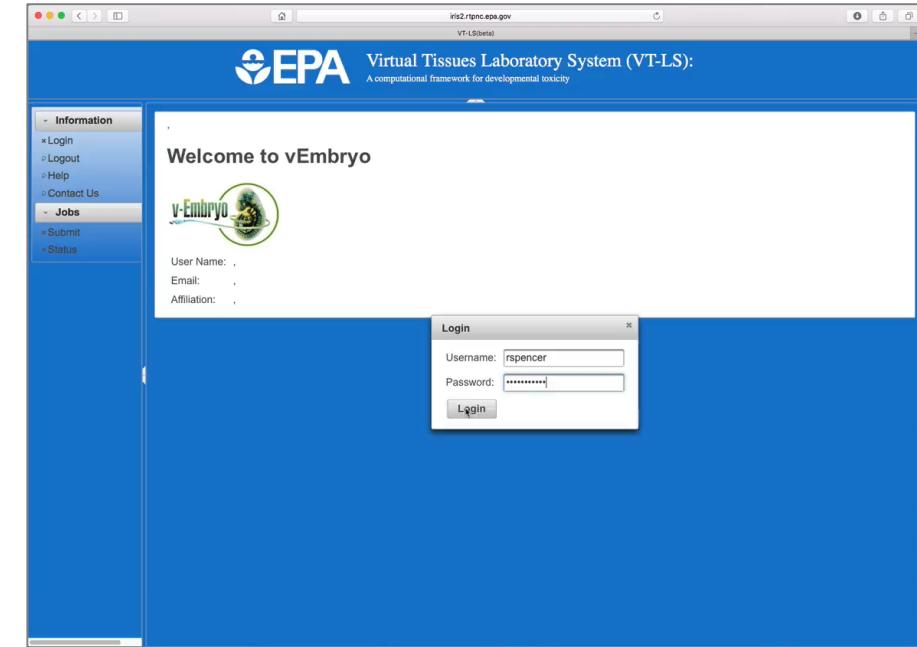
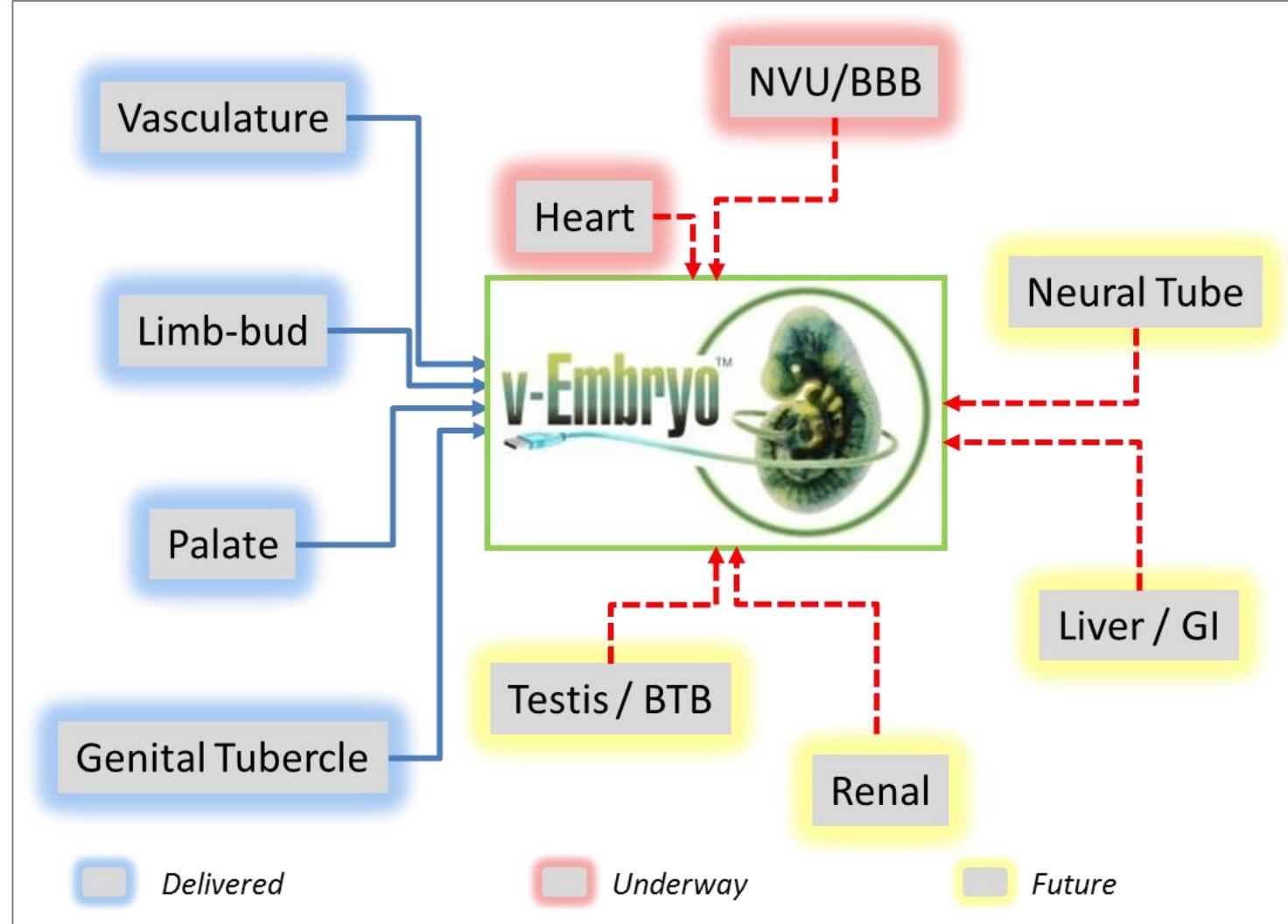
Endothelial Stalk:	
Endothelial Tip:	
Macrophage:	
Mural:	

NPC:	
Microglia:	
Pericyte:	
Astrocyte:	

- BBB morphogenesis
- microglial sensing
- AOP for microcephaly
- ToxCast predictions
- human brain mimics

POSTERS 13 & 14

Virtual Tissues Laboratory System (VT-LS)



- access to ABMS
- VT-KB (knowledgebase)
- text-mining tools and resources
- high-performance computing

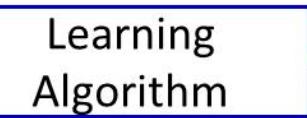
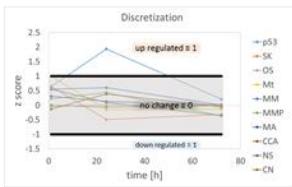
See VTLS demo

Tipping Points: state trajectories that distinguish cellular adaptive vs adverse reactions.

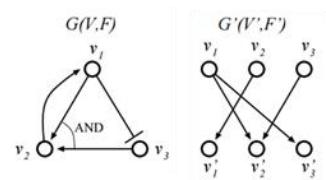


	p53	SK	OS	Mt	MM	MMP	MA	CCA	NS	CN
1h	0.64	0.65	-0.04	1.00	0.55	0.23	0.31	-0.13	0.55	0.00
24h	1.94	-0.49	0.02	-0.16	0.61	0.44	0.13	0.39	0.10	-0.06
72h	0.21	-0.32	-0.01	-0.13	0.01	-0.36	0.01	-0.06	-0.36	-0.02

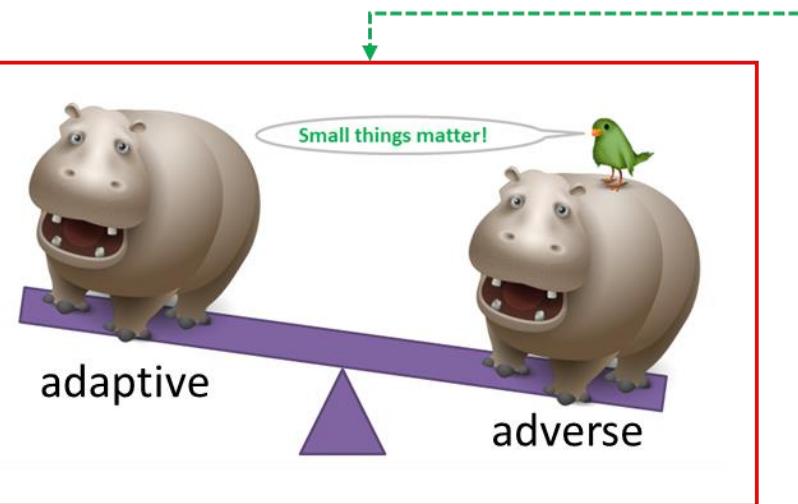
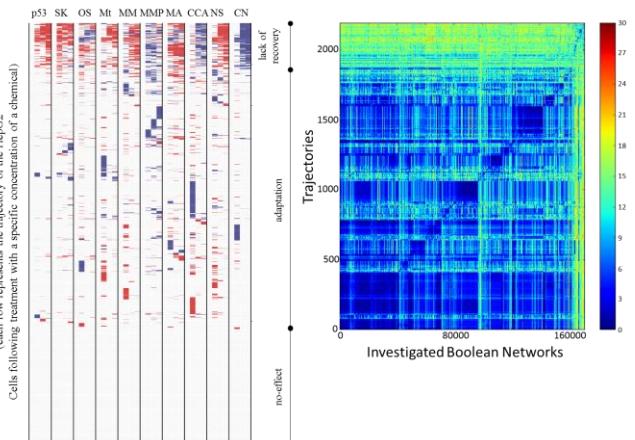
	p53	SK	OS	Mt	MM	MMP	MA	CCA	NS	CN
1h	0	0	0	0	0	0	0	0	0	0
24h	1	0	0	0	0	0	0	0	0	0
72h	0	0	0	0	0	0	0	0	0	0



```
for i = 1 to n do
    count ← 0;
    for all combinations of K nodes ( $v_1, \dots, v_K$ ) do
        for all Boolean function f with K inputs do
            mismatch ← 0;
            for j = 1 to m do
                if  $O_j(v_i) \neq f_j(I_j(v_1), \dots, I_j(v_K))$  then
                    mismatch ← mismatch + 1;
            if mismatch < θ - m then
                output f( $v_1, \dots, v_K$ ) as a function
                assigned to  $v_i$ ; count ← count + 1;
            if count ≠ 1 then
                output "NOT IDENTIFIED" and halt;
```

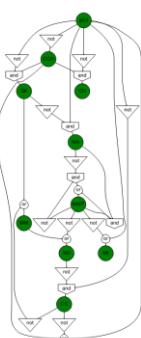
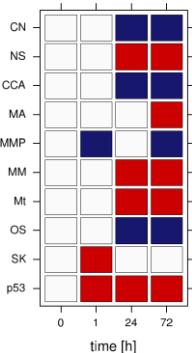


State trajectories



Attractors

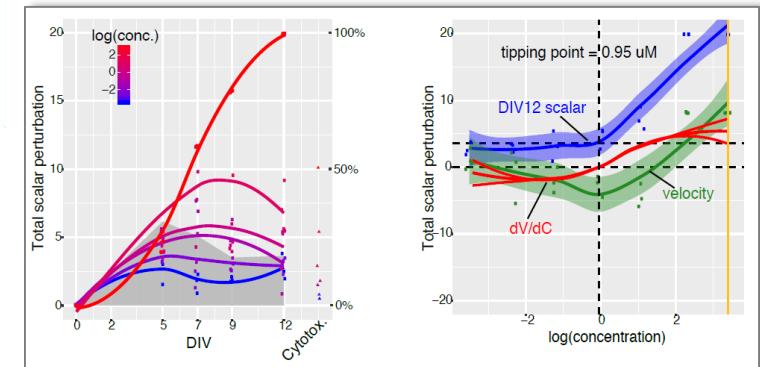
endpoints



State Transition Table

INPUT					
v_1	v'_1	v_2	v'_2	v_3	v'_3
0 0 0	0	0	0	1	
0 0 1	0	0	0	1	
0 1 0	1	0	0	1	
0 1 1	1	0	0	1	
1 0 0	0	0	0	0	
1 0 1	0	1	0	0	
1 1 0	1	0	0	0	
1 1 1	1	1	0	0	

Synaptic coupling



POSTER 16

Integration with OCM-PT STAR Centers



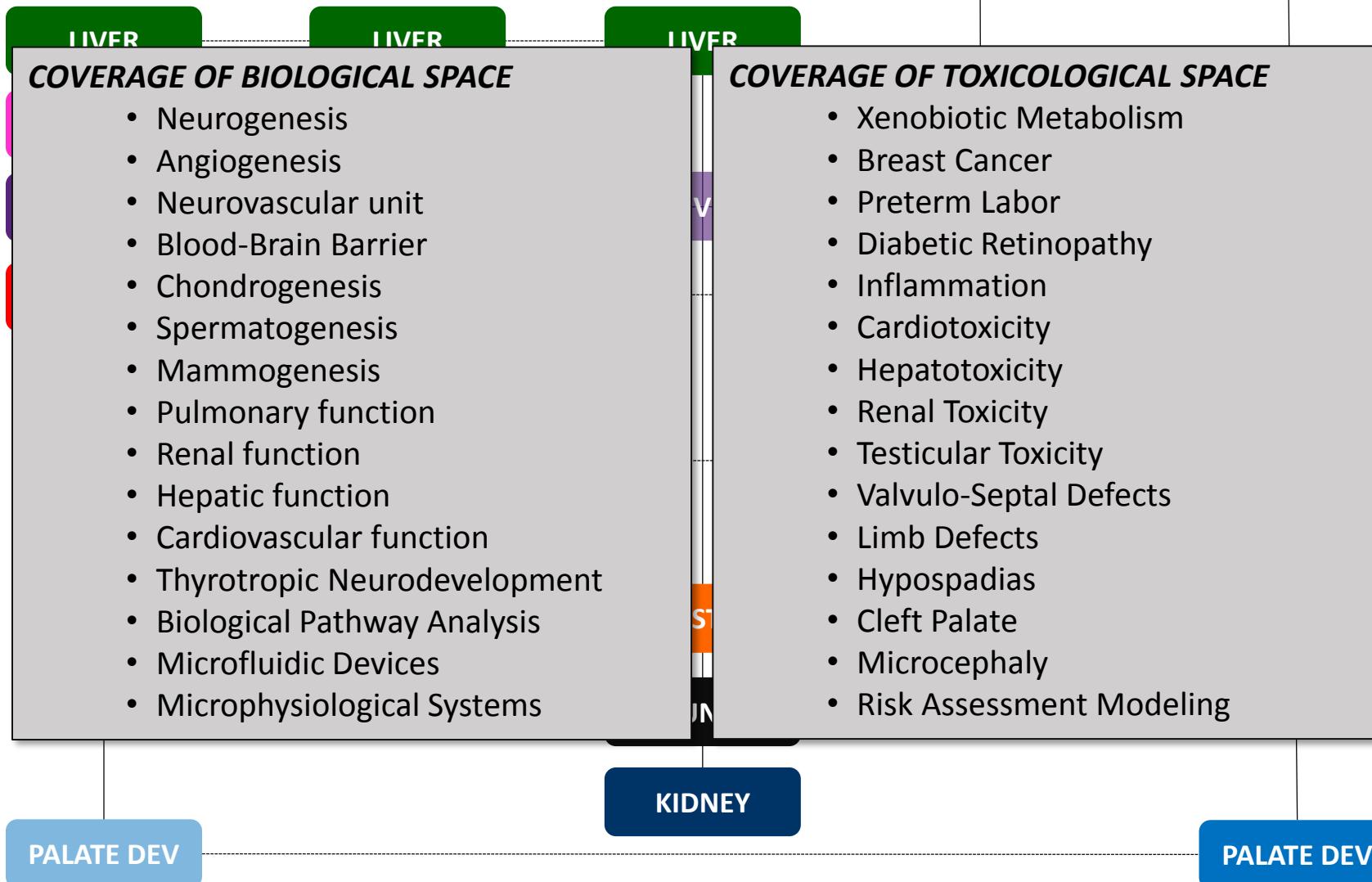
Univ. Wisconsin
W Murphy - PI

Vanderbilt-Pitt
S Hutson- PI

U Washington
E Faustman - PI

Texas A&M
I Rusyn - PI

VMs
CSS 17.02





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B Abbott*
D Belair^
K Das
C Wolf
C Wood

NHEERL/RCU

A Fisher
R Grindstaff
W Padgett
H Ren
A Swank
W Winnik

EMVL

R Spencer
I Balabin
T Cathy
T Howard
T Transue

NERL

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C Mazur
S Marchitti^

NCCT

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A Schwab
T Tal
P Wages

CSS

T Bahadori
J Cowden
J Franzosa
J Kenneke
S Ramasamy

EXTERNAL

S Hutson (Vanderbilt U) – VPROMPT
J Brown (Vanderbilt U) – VPROMPT
J Wikswo (Vanderbilt U) - VPROMPT
W Murphy (U Wisconsin) – HMAPS
W Daly (U Wisconsin) – HMAPS
E Nguyen (U Wisconsin) – HMAPS
E Faustman (U Washington) – UW-PTC
I Rusyn (Texas A&M) – CT-AOP
S Bhattacharya (Michigan State U)
F Ginhoux (Singapore) - A*STAR
J Palmer (Stemina)
S Stice (ArunA)
B Cai (Vala)