Virtual Tissues and Developmental Systems Biology

Thomas B. Knudsen, PhD
National Center for Computational Toxicology
US Environmental Protection Agency
Research Triangle Park NC 27711
Gordon Research Conference, July 31, 2008

Background

- embryogenesis entails a genomic program that orchestrates precise aggregate cell behaviors across time and space

- *core developmental processes* (Bard, 2008):

  patterning: sets up future events leading to body structures

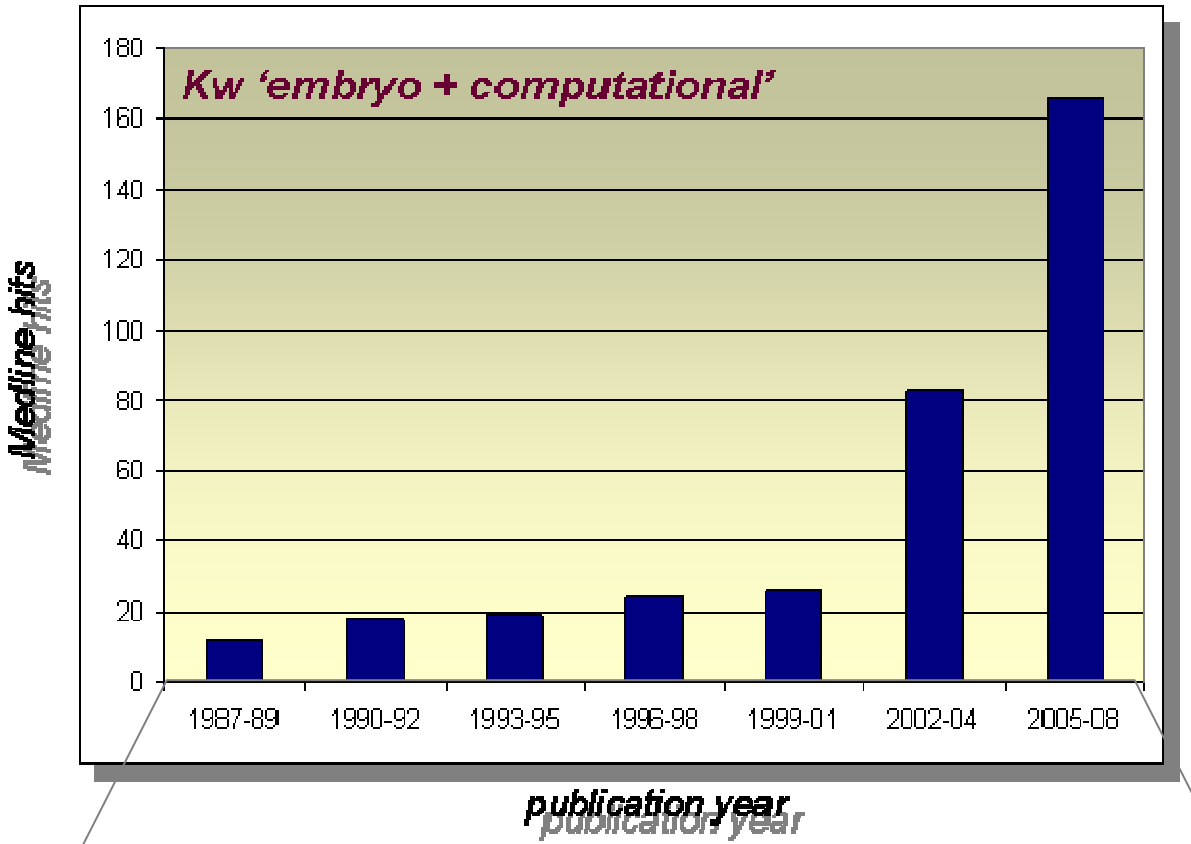
  morphogenesis: tissue rearrangements and movements

  proliferation and apoptosis: basis of selective growth and shaping

  cell differentiation: generation of distinct cell types

- virtual tissues: computational (*in silico*) framework for modeling key aspects of this complex biology

Computational embryology:
impact of the human genome project



descriptive biology ← cell biology biochemistry | molecular biology | genomics bioinformatics | systems biology → *virtual biology*

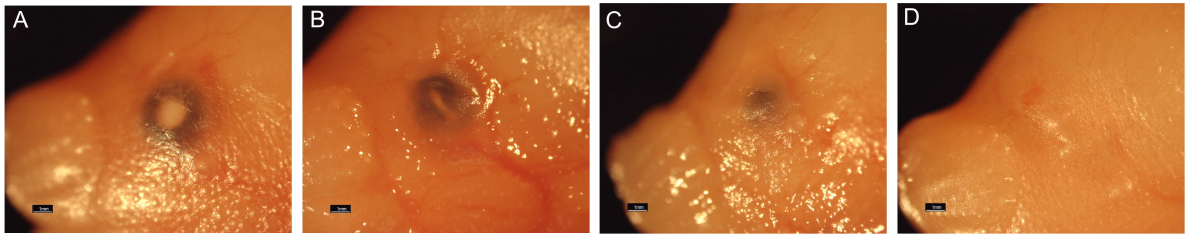
Research goals

- computational modeling of embryonic systems to analyze how '*core developmental processes*' are wired together
- knowledgebase (KB) of facts and concepts focused on developmental health and disease
- simulation engine (SE) for multi-scale models to help understand and eventually predict developmental defects
- has the potential to address environmental and human health factors with broad scientific and economic impacts

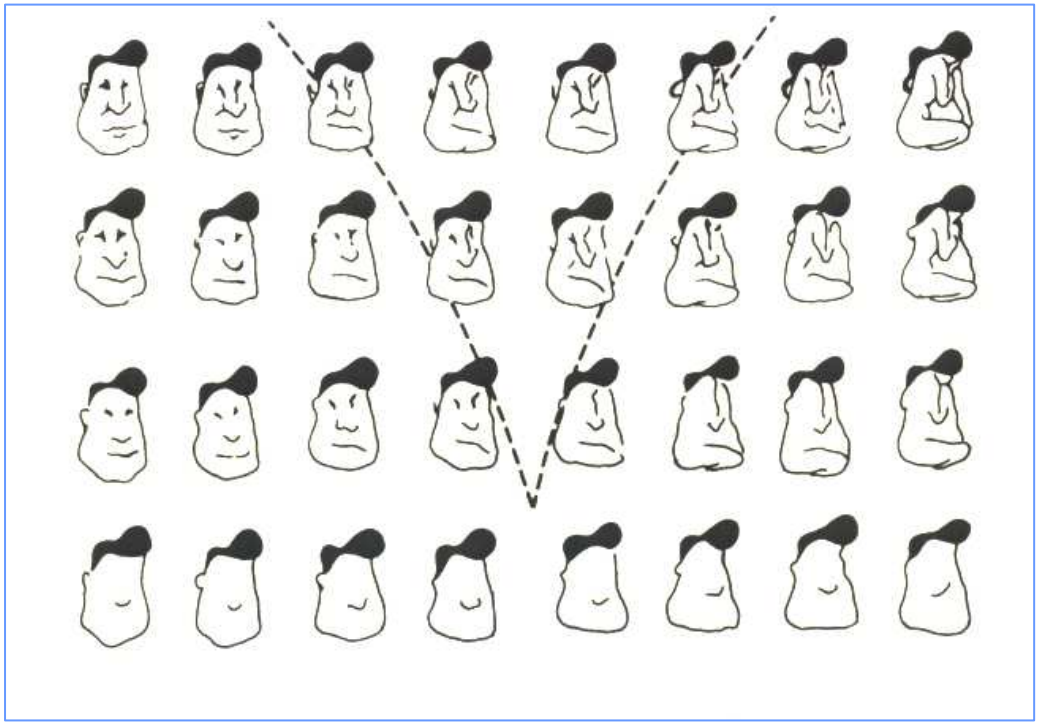
Modeling catastrophe *in silico*

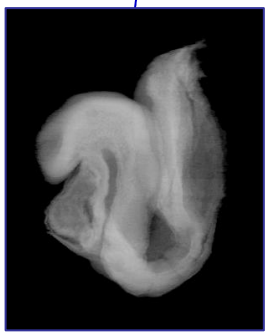
small changes in nonlinear system → sudden shifts in behavior

STATE A ◄----------► **STATE B**



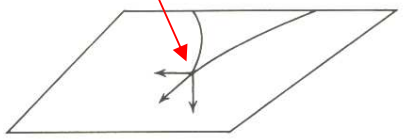
Gestation →

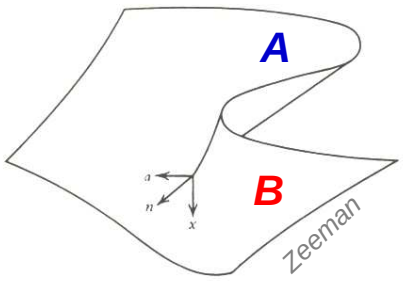




exposure

critical point

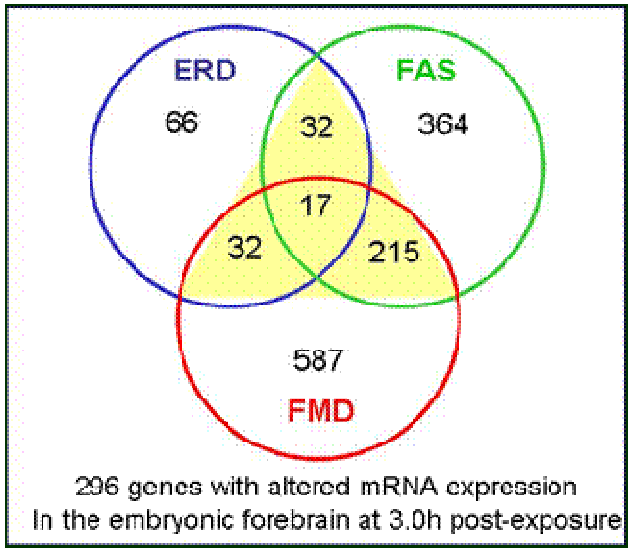




SOURCE: Saunders, 1980, Cambridge University Press NY

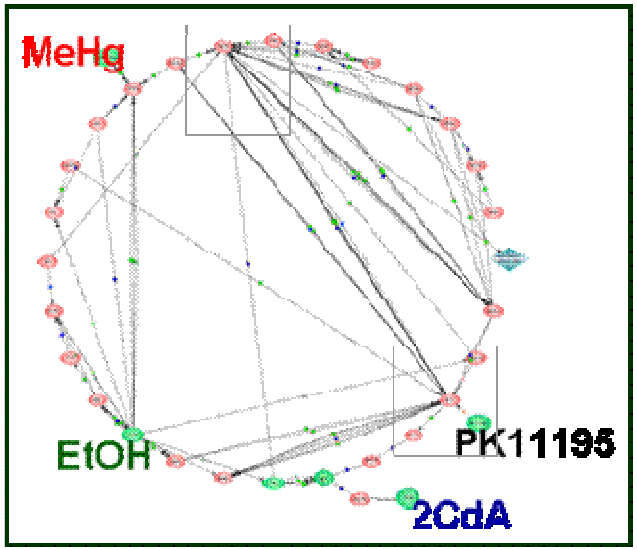
Genomic analysis of a *critical point*

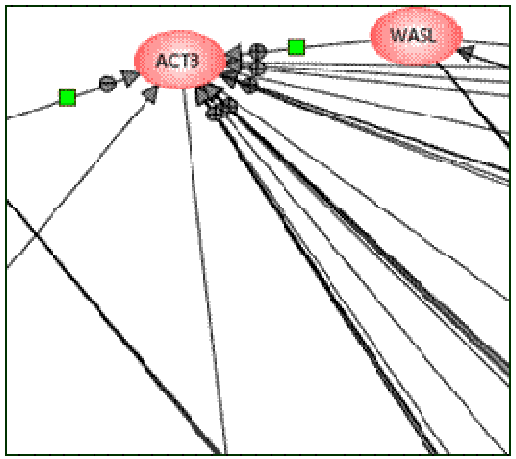
rudimentary forebrain 3-6h after chemical exposure

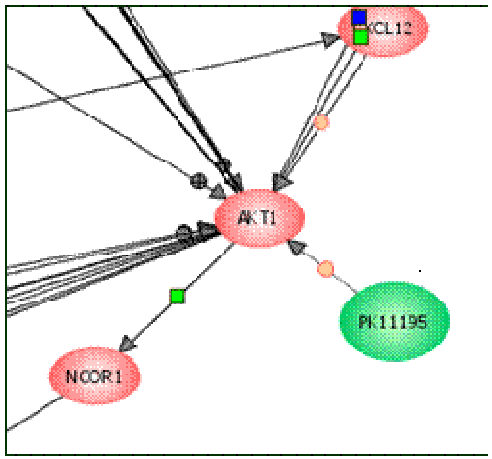


296 genes with altered mRNA expression
In the embryonic forebrain at 3.0h post-exposure

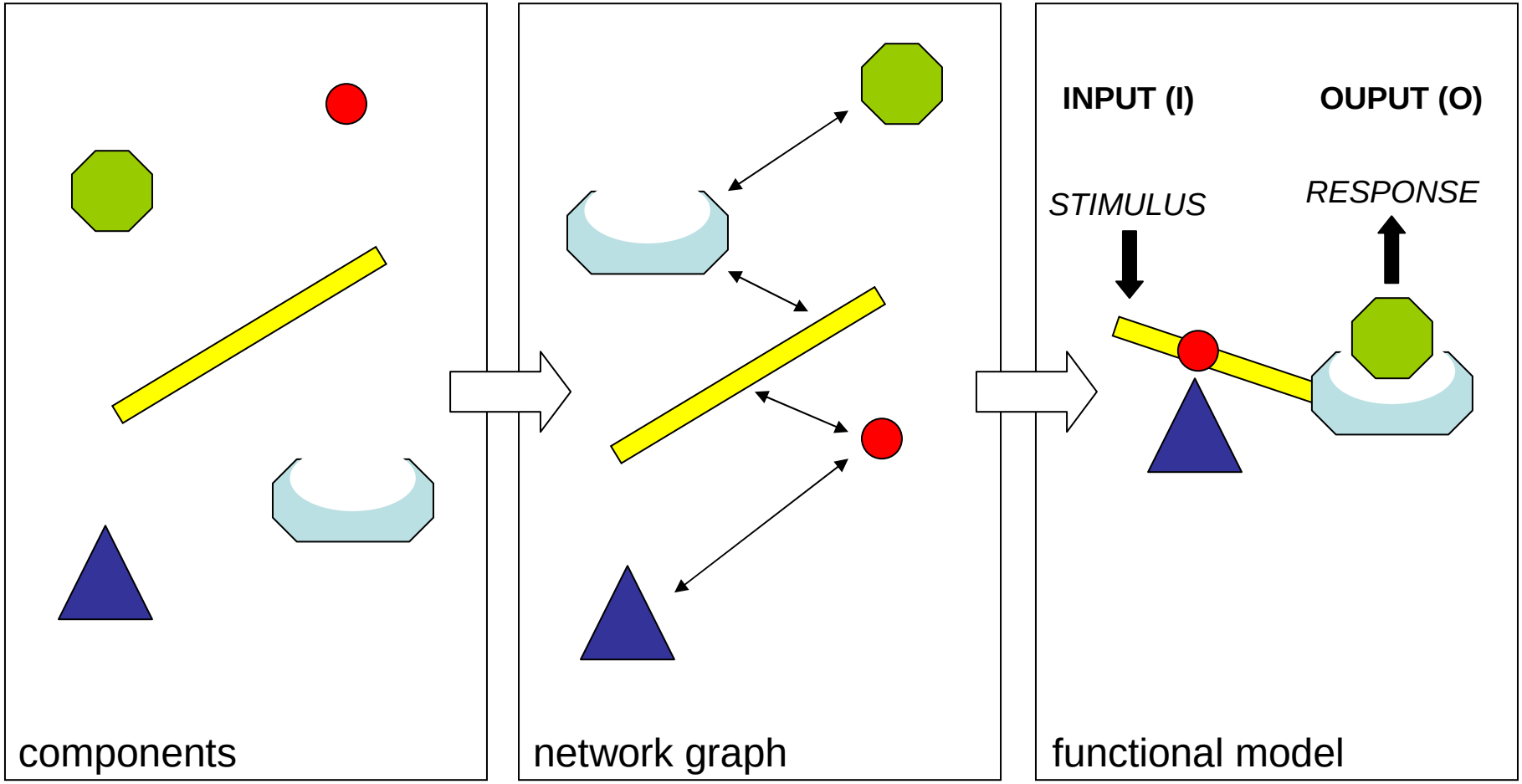
KEGG PATHWAY	*LIST*	*P value*
RIBOSOME	55	2.52E-06
FOCAL ADHESION	41	0.010225
CALCIUM SIGNALING PATHWAY	36	0.006316
INSULIN SIGNALING PATHWAY	27	0.034363
PHOSPHATIDYLINOSITOL SIGNALING SYSTEM	23	0.005534
GAP JUNCTION	20	0.037796
LONG-TERM DEPRESSION	18	0.016329
ADHERENS JUNCTION	17	0.045554
GLYCOLYSIS / GLUCONEOGENESIS	16	0.011854
LONG-TERM POTENTIATION	15	0.029993
PROTEASOME	12	0.003279
TYPE II DIABETES MELLITUS	12	0.028197





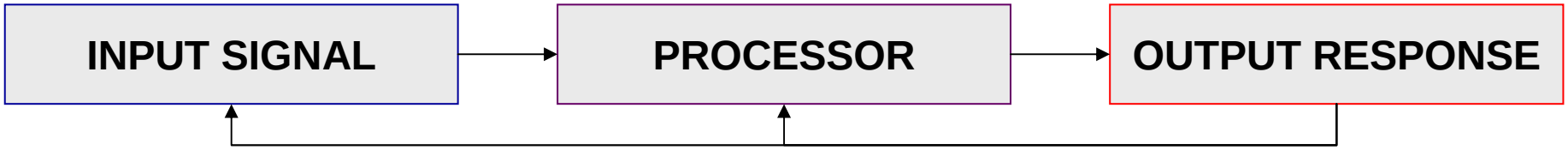


General systems models



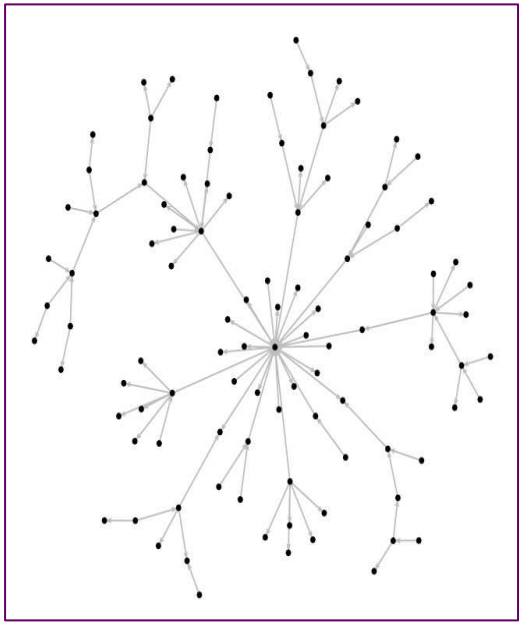
Based on MW Covert (2006) Integrated regulatory and metabolic models. In: Computational Systems Biology, edited by A Kriete and R Eils, Elsevier Academic Press (page 194)

Gene regulatory networks (GRNs):
information processing machines of the cell



Developmental Signals

Wnt, TGFβ, Shh, RTK, Notch-Delta, NF-kB, PCD, nuclear hormone receptors, RPTPs, receptor GC, cytokines, NO, GPCRs, integrins, CADs, gap junction, ligand-gated cation channels, UPR, p53



Morphoregulatory Responses

patterning
proliferation
apoptosis
differentiation
adhesion
motility
shape
ECM remodeling

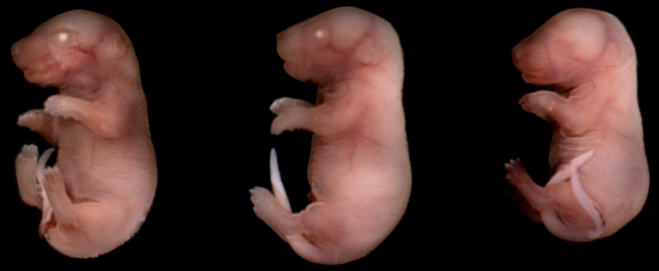
In the new research vision …

… our ability to create mathematical models describing the function of biological networks will become just as important as traditional lab skills and thinking - D Butler (2001) Nature 409, 758-760

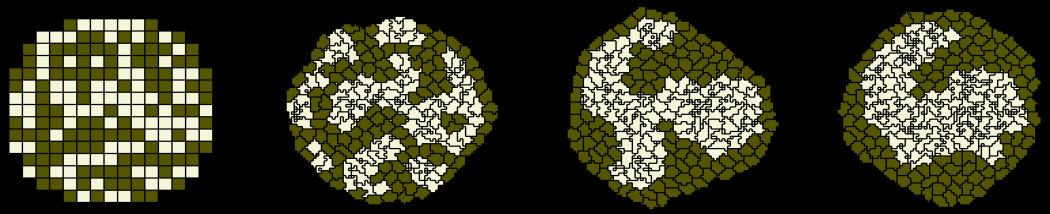
"Molecular biology took Humpty Dumpty apart … mathematical modeling is required to put him back together again …"

– Schnell et al. (2007) Am Sci 95:134

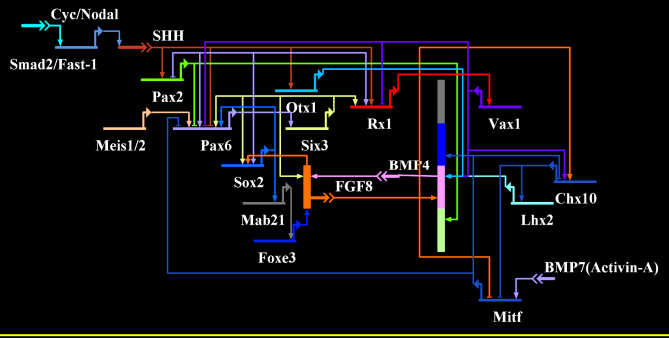
traditional prenatal studies



artificial life simulators



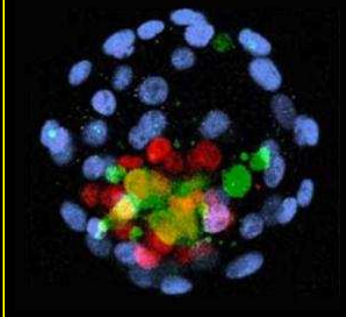
developmental pathways



v-Embryo

HTP screening assays

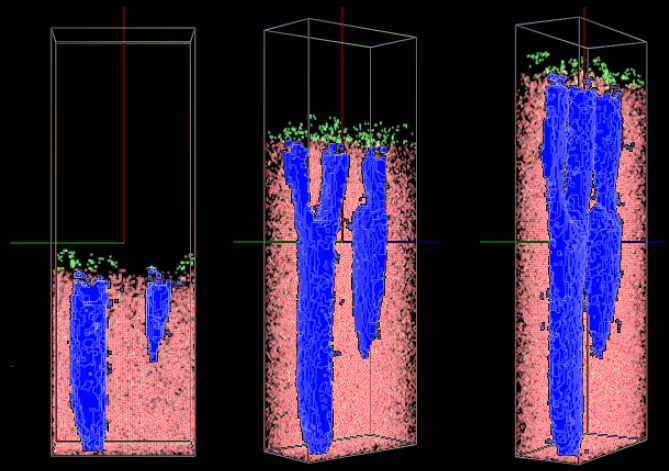
stem cells



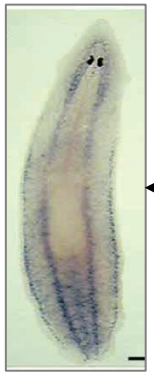
Z-fish embryos

ToxCast™ & BDSM

in silico morphogenesis (CC3D)



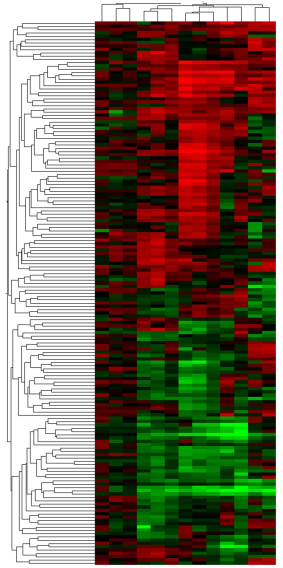
Consequences of perturbing GRNs
illustrated in the master gene for eye development



monophyletic

Pax6

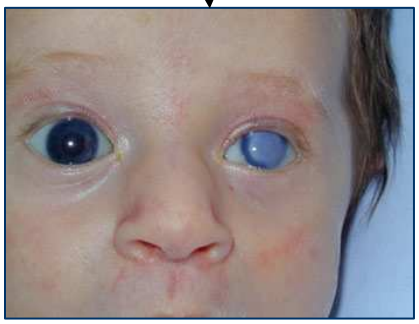
teratogenesis



overexpression

underexpression

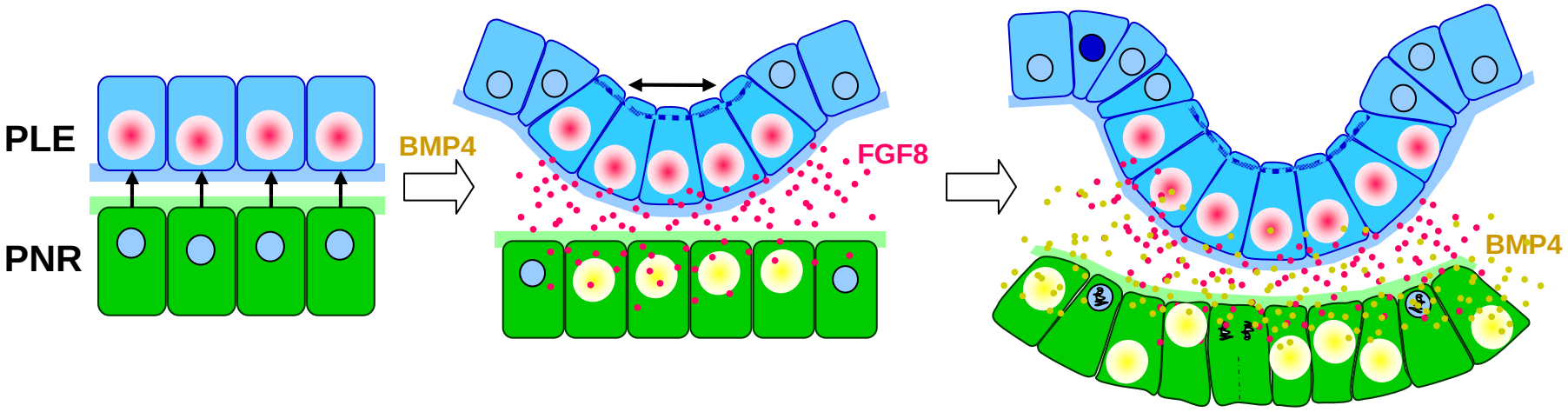
mutation



Early eye development

cell-based processes driving the natural system

PATTERNING	MORPHOGENESIS	SELECTIVE GROWTH	CELL DIFFERENTIATION
cell interaction	cytoskeletal remodeling	proliferation and apoptosis	crystallins, Photorec. genes

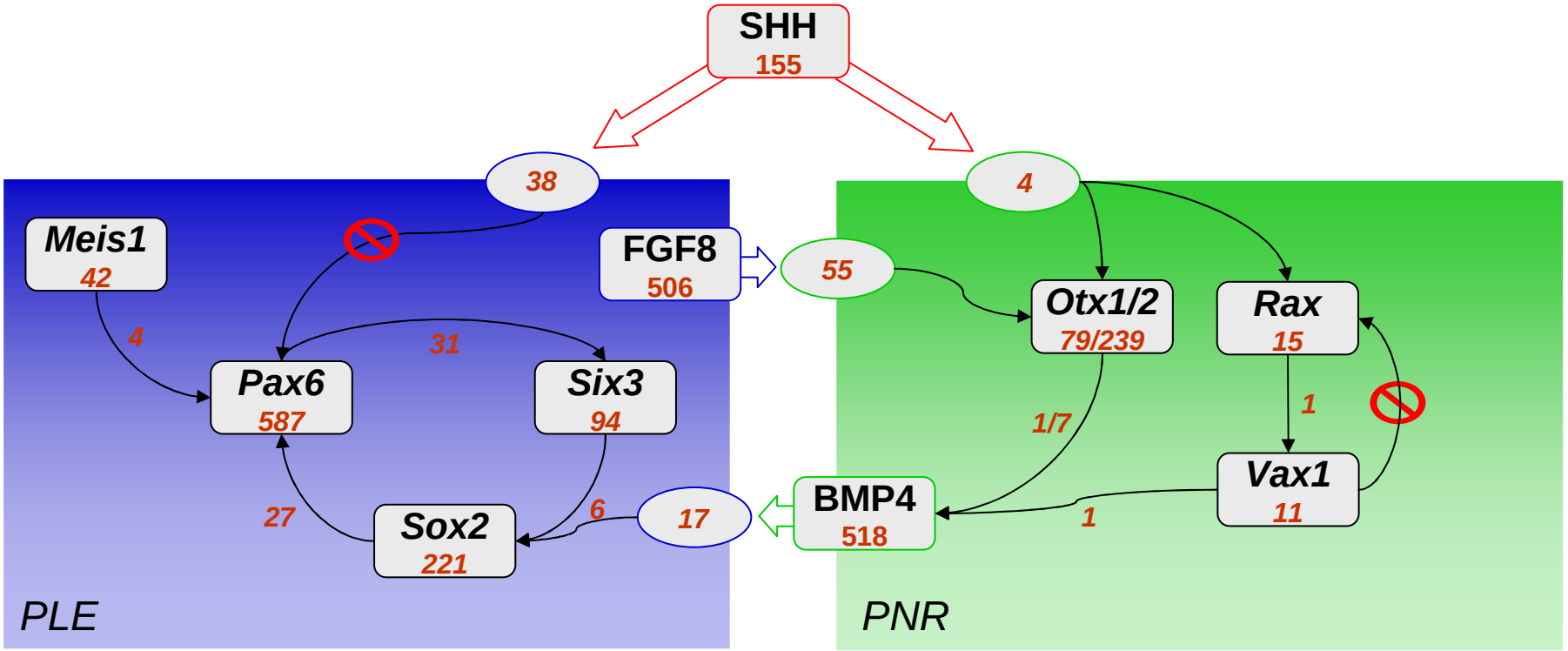


cell-based processes driving the formal system

NETWORK LOGIC	CELLULAR AUTOMATA	AGENT FIELDS	PHASE TRANSITIONS
information flow	discrete state machines	signal-response gradients	trajectories to cell types

Self-regulating gene network:

3954 PMIDs mouse, rat, zebrafish, human eye development

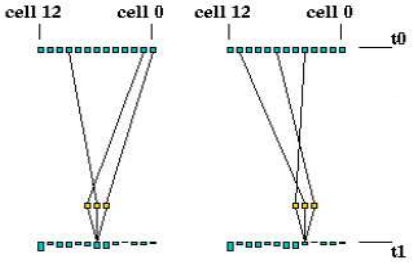


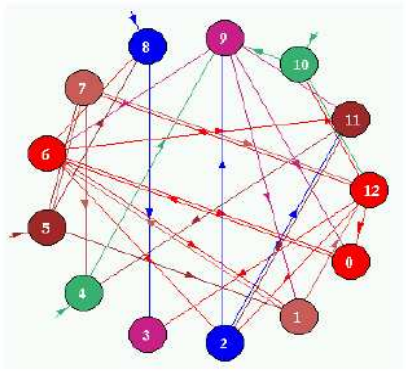
7 transcription factors
3 receptor systems
3 signal ligands

network size (n) = 13 nodes
network connectivity (k) = 3
Boolean states (2^n) = 8192

Discrete Dynamical Networks (DDNs)

		2.	1.	0.	rule(hex)
7	12..	10	1	7	56
2	11..	6	2	9	04
4	10..	10	10	12	c4
4	9..	2	10	4	34
2	8..	5	6	8	ea
3	7..	12	5	12	64
5	6..	1	9	0	06
5	5..	5	7	5	64
2	4..	4	11	7	06
0	3..	8	12	12	5e
2	2..	11	6	12	4a
2	1..	6	5	9	d6
1	0..	12	9	6	bc





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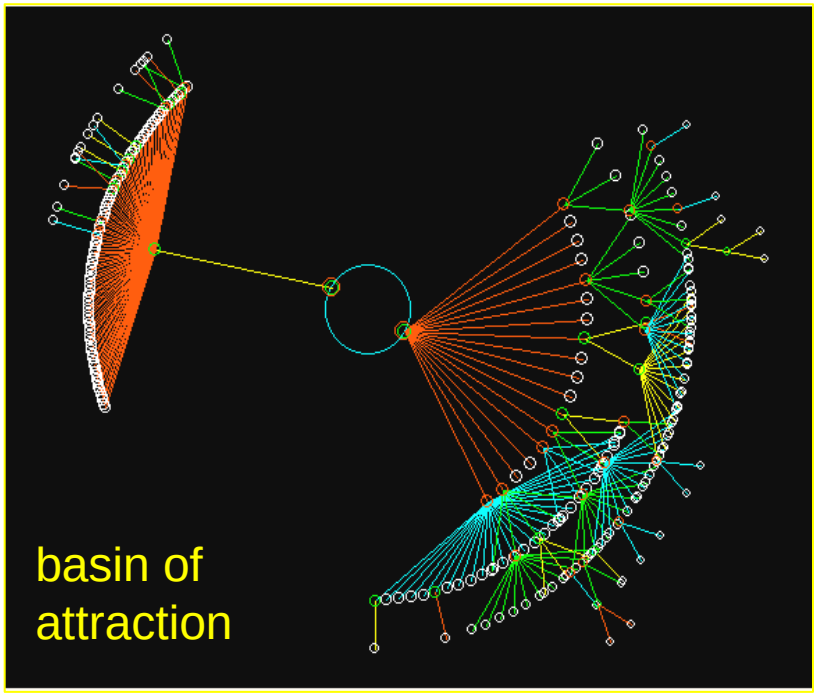
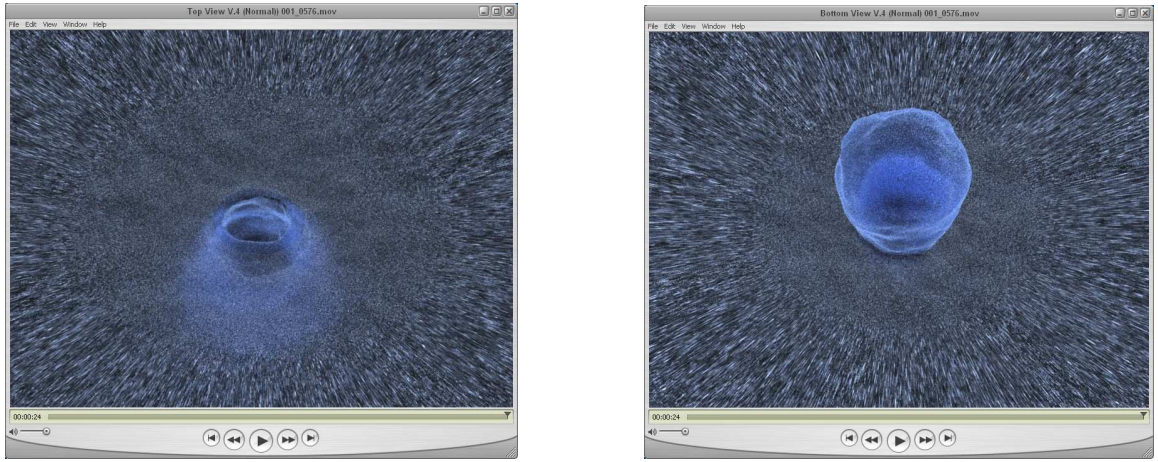


DDNs: ‘state machines’ to analyze GRN trajectories following chemical exposure:

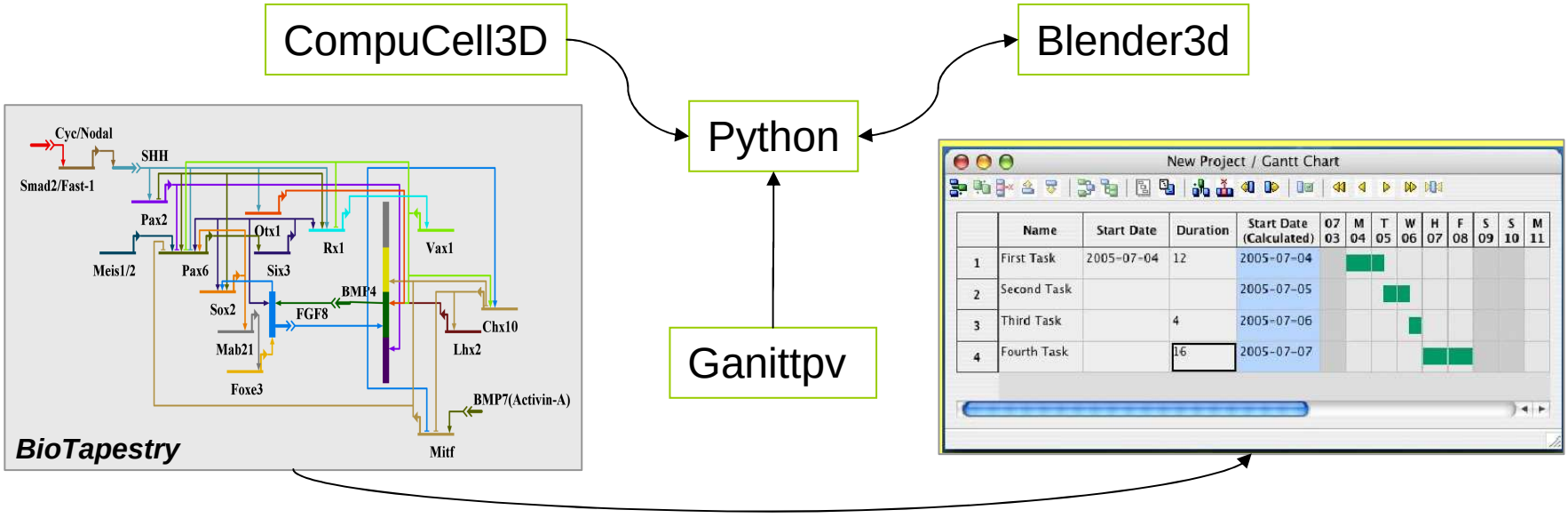
- run network forward to find attractor states
- run backwards to disclose historical paths

MODEL: DDLab (A Wuensche, http://www.ddlab.org)

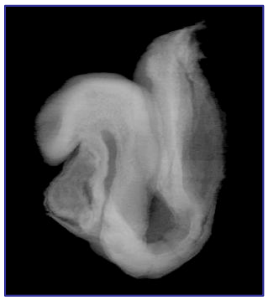
Executable *(in silico)* model:
lens vesicle abstracted from mouse embryos



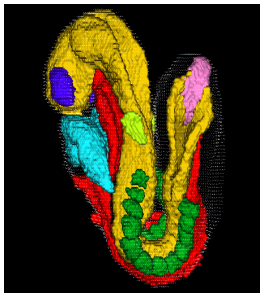
prototype: 72h period of initial lens development



In silico teratogenesis: prototype being developed for v-Embryo™

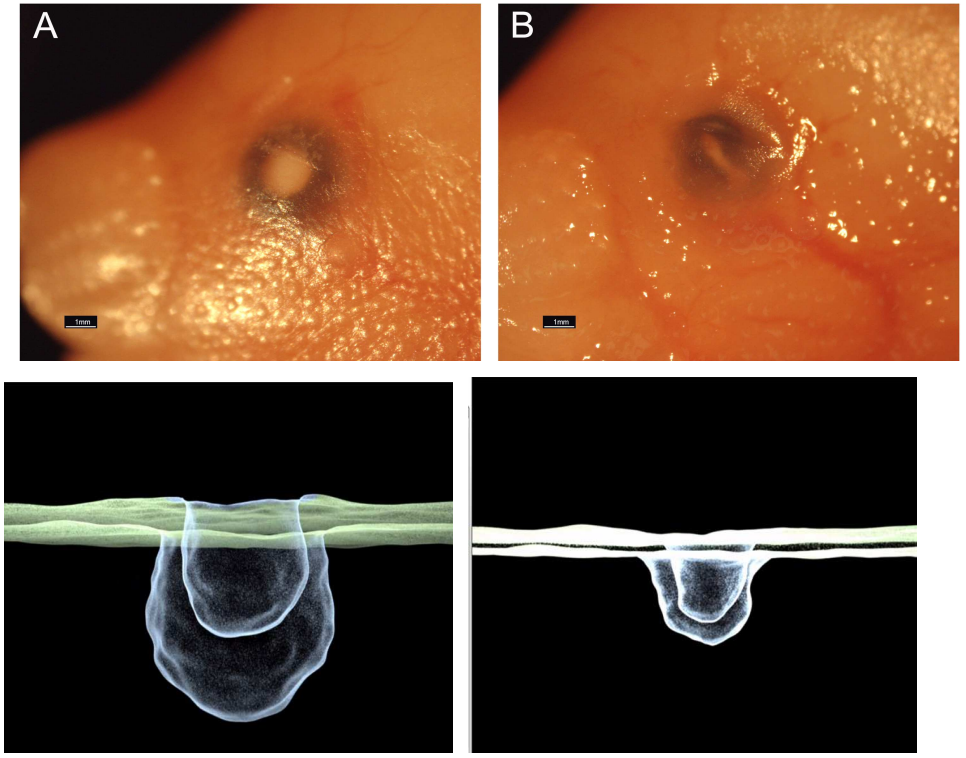


Day 8
exposure



Day 17
in vivo

Day 11
in silico



eye defects produced *in vivo* and *in silico* following altered signaling of the lens placode (day 8)

Summary

- virtual tissues and artificial life simulators as models to study morphogenesis and predict defects *in silico*
- systems-based approach integrates vast amounts of data with computational (*in silico*) models
- models address how mechanisms at one scale (cellular) can interact to produce higher level (tissue) phenomena
- myriad of agents that disrupt development calls for systems-level understanding of dynamical networks

Acknowledgements

University of Louisville

Caleb Bastian
Maia Green
Ken Knudsen
Reetu Singh
Nafeesa Owens
Bruno Ruest
Amar Singh
Reetu Singh

NCCT/EPA

Jerry Blancato
David Dix
Keith Houck
Richard Judson
Bob Kavlock
Matt Martin
Imran Shah
Amar Singh (LHM)
Michael Rountree
Richard Spencer (EMVL)
Sid Hunter (NHEERL)

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Grant sponsors

RO1 ES09120 (NIEHS)
RO1 AA13205 (NIAAA)
R21 ES13821 (NIEHS)
P30 ES014443 (NIEHS)

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