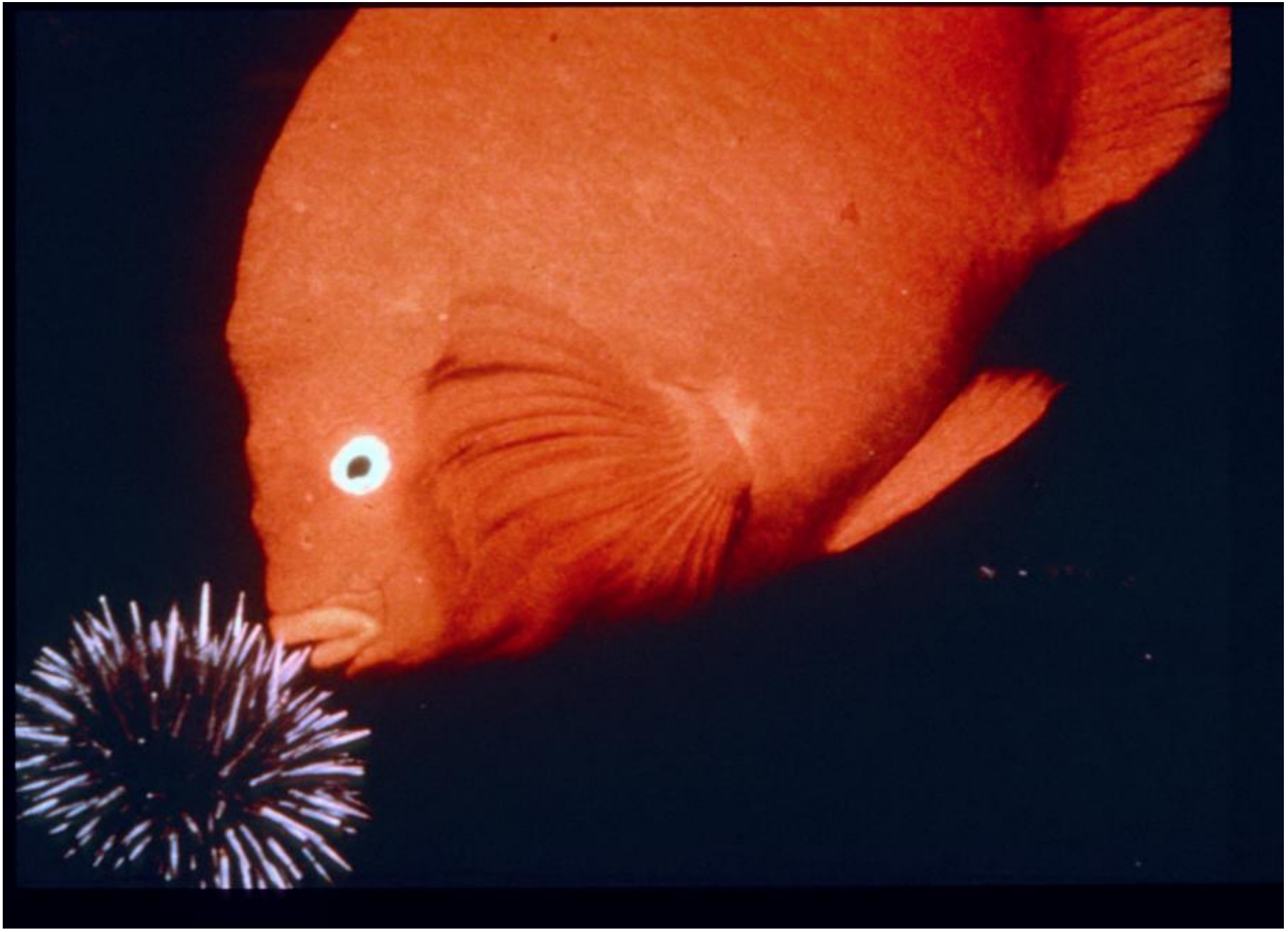
ENCODED NETWORK LOGIC FOR EMBRYONIC DEVELOPMENT

KITP

AUGUST 2013

Eric Davidson, Caltech Aug 9, 2013 KITP Morpho13



DIVERSE BODY PLANS ARISE FROM DIVERSE GENOMIC REGULATORY PROGRAMS USING

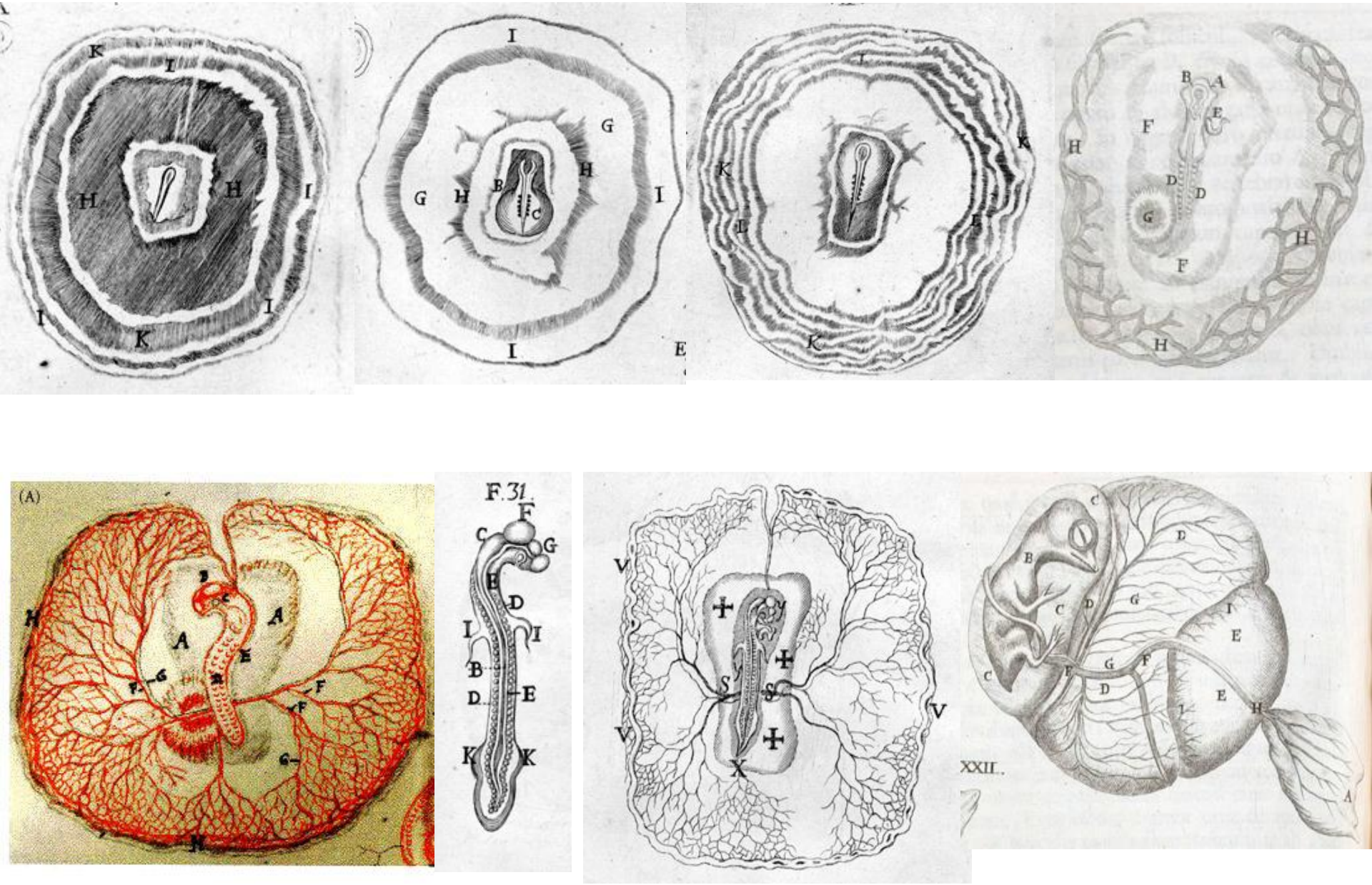
-SIMILAR REGULATORY GENE REPERTOIRES

-SIMILAR DEVELOPMENTAL GENE CONTROL MECHANISMS

-SIMILAR PRINCIPLES BY WHICH THE GENOMIC CODE IS TRANSFORMED INTO DEVELOPMENTAL PHENOMENA

-BUT THE PROGRAMS FOR SPATIAL ALLOCATION OF REGULATORY STATE ARE UNIQUE TO EACH CLADE

THE PROGRAM INSURES THAT WITHIN EACH SPECIES THE OUTCOME IS EXTREMELY REPRODUCIBLE, IT OPERATES OVER AND OVER AGAIN IN THE SAME WAY..



Marcello Malpighi 1685

MORPHOLOGY AND THE UNDERLYING ARRAYS OF SPATIAL REGULATORY STATES INCREASE IN COMPLEXITY AS THE PROGRAM OPERATES

A FEW GENERAL COMMENTS ABOUT THE HERITABLE GENOMIC PROGRAMS THAT DIRECT THE UNIQUE PROCESS OF DEVELOPMENT

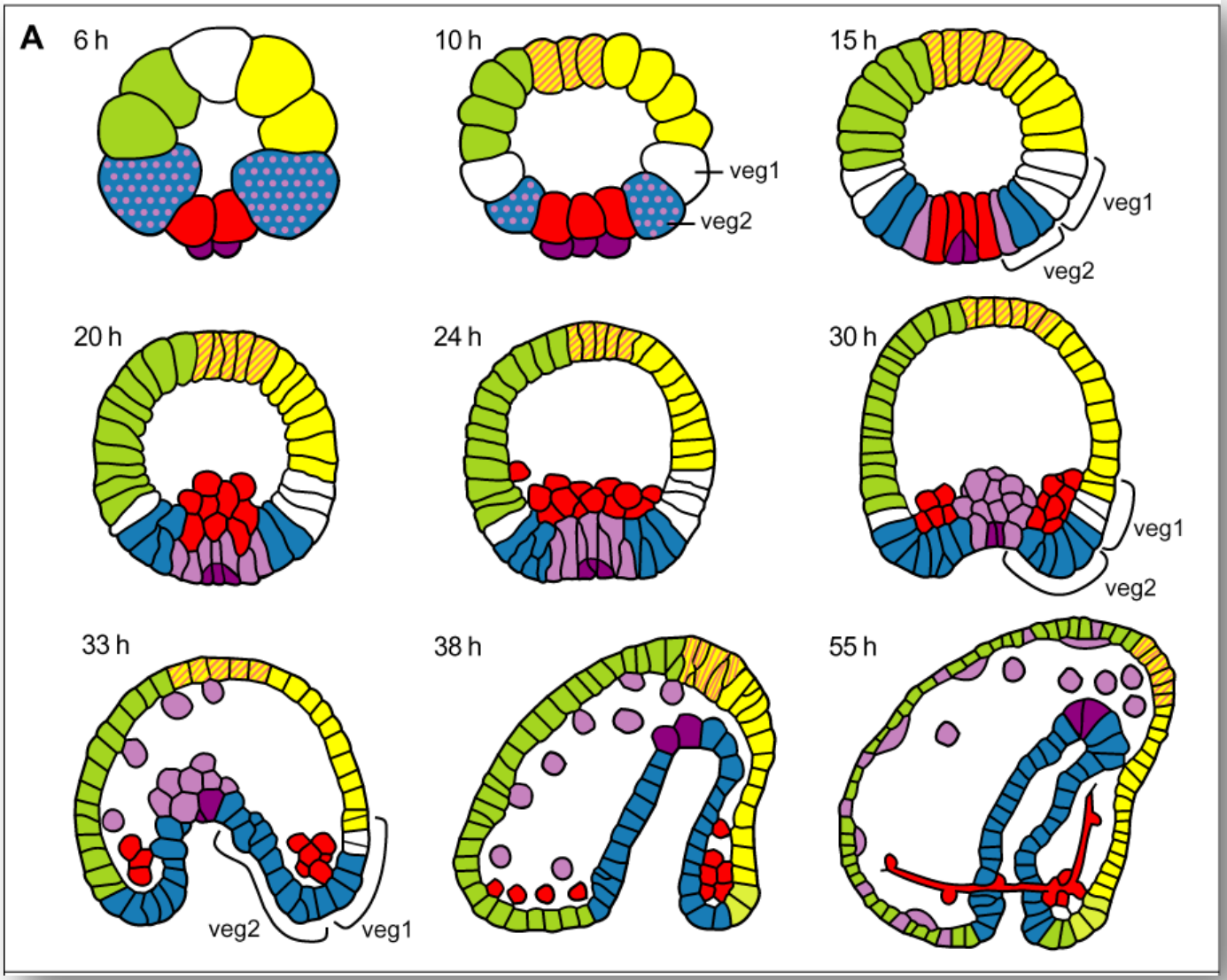
….

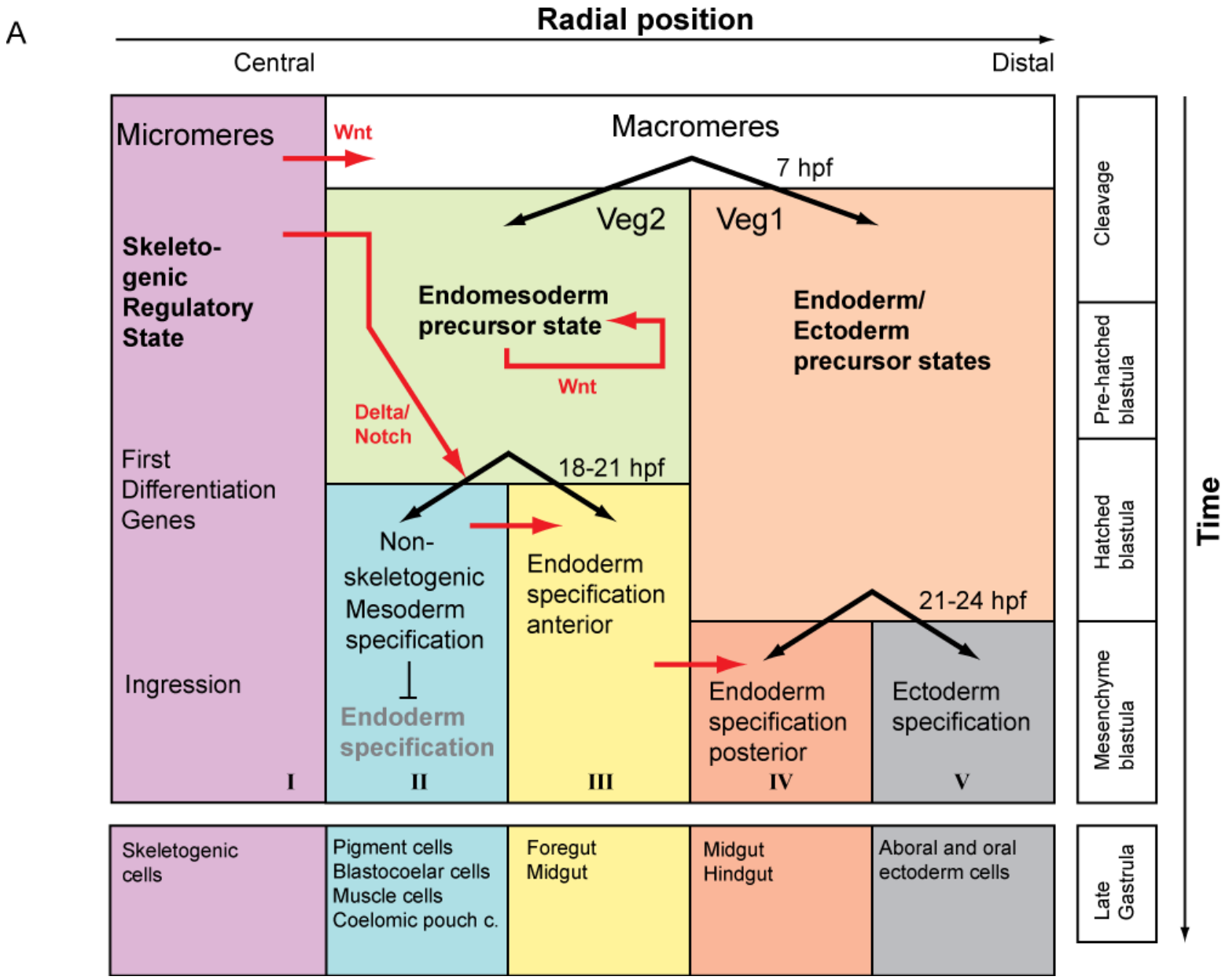
DEVELOPMENT OF THE ANIMAL BODY PLAN IS ENCODED BY SPATIAL GENE REGULATORY PROGRAMS

THESE PROGRAMS ARE HARDWIRED IN THE REGULATORY GENOME; THEY ARE HIERARCHICAL AND THEY OPERATE UNIDIRECTIONALLY

THESE PROGRAMS FUNCTION BY SUCCESSIVE INSTALLATION OF SPATIAL REGULATORY STATES (SETS OF TRANSCRIPTION FACTORS OPERATIVE IN GIVEN CELLS)

SPECIFICATION IN THE SEA URCHIN EMBRYO




A
Radial position
Central
Distal
Micromeres
Wnt
Macromeres
7 hpf
Veg2
Veg1
Skeleto-
genic
Regulatory
State
Endomesoderm
precursor state
Wnt
Endoderm/
Ectoderm
precursor states
Delta/
Notch
First
Differentiation
Genes
18-21 hpf
Non-
skeletogenic
Mesoderm
specification
Endoderm
specification
anterior
21-24 hpf
Ingression
Endoderm
specification
posterior
Ectoderm
specification
Endoderm
specification
I
II
III
IV
V
Cleavage
Pre-hatched
blastula
Hatched
blastula
Mesenchyme
blastula
Late
Gastrula
Time
Skeletogenic
cells
Pigment cells
Blastocoelar cells
Muscle cells
Coelomic pouch c.
Foregut
Midgut
Midgut
Hindgut
Aboral and oral
ectoderm cells

THE SEA URCHIN EMBRYO GRN'S:

NOW INCLUDE > 90 REGULATORY GENES IN VARIOUS EMBRYONIC TERRITORIES EXPRESSED SPECIFICALLY UP TO GASTRULATION (30H)

EXPERIMENTALLY BASED ON:
(1) HIGH RESOLUTION SPATIAL (3H) & TEMPORAL (1H) EXPRESSION DATA
(2) VERY LARGE SCALE MATRIX OF PERTURBATION RESULTS
(3) EXTENSIVE CIS-REGULATORY ANALYSES

THOUGH TODAY I WILL DISCUSS ONLY THE ENDOMESODERMAL GRN, NEW GRNS ENCODING ORAL & ABORAL MESODERM ARE ALSO NEARING COMPLETION, AND WE LOOK FORWARD TO UNDERSTANDING THE GRN CODE FOR THE WHOLE EMBRYO

THE POINT IS TO DISCOVER WHAT ENCODED INPUTS CAUSE EACH GENE TO TURN ON & OFF

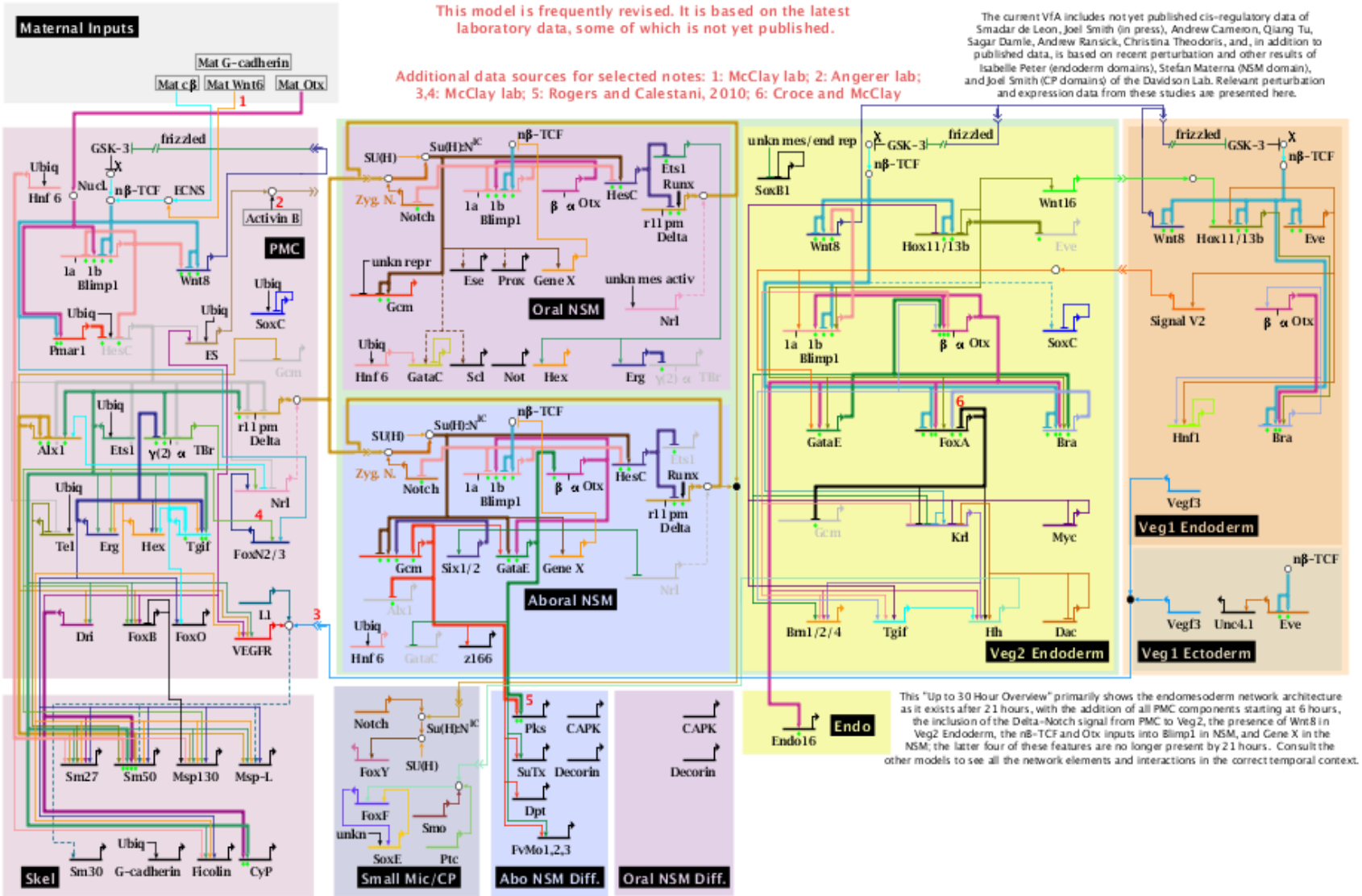
Endomesoderm Specification up to 30 Hours

November 21, 2011

This model is frequently revised. It is based on the latest laboratory data, some of which is not yet published.

The current VfA includes not yet published cis-regulatory data of Smadar de Leon, Joel Smith (in press), Andrew Cameron, Qiang Tu, Sagar Damle, Andrew Ransick, Christina Theodoris, and, in addition to published data, is based on recent perturbation and other results of Isabelle Peter (endoderm domains), Stefan Materna (NSM domain), and Joel Smith (CP domains) of the Davidson Lab. Relevant perturbation and expression data from these studies are presented here.

Additional data sources for selected notes: 1: McClay lab; 2: Angerer lab; 3,4: McClay lab; 5: Rogers and Calestani, 2010; 6: Croce and McClay



This "Up to 30 Hour Overview" primarily shows the endomesoderm network architecture as it exists after 21 hours, with the addition of all PMC components starting at 6 hours, the inclusion of the Delta-Notch signal from PMC to Veg2, the presence of Wnt8 in Veg2 Endoderm, the nß-TCF and Otx inputs into Blimp1 in NSM, and Gene X in the NSM; the latter four of these features are no longer present by 21 hours. Consult the other models to see all the network elements and interactions in the correct temporal context.

Ubiq=ubiquitous; Mat = maternal; activ = activator; rep = repressor; unkn = unknown; Nucl. = nuclearization; χ = β-catenin source; nβ-TCF = nuclearized b-β-catenin-Tcf1; ES = early signal; ECNS = early cytoplasmic nuclearization system; Zyg. N. = zygotic Notch

In this brief talk I have two main objectives:

I shall use a recently constructed Boolean logic model of the sea urchin embryo GRN

1) To ask whether the GRN suffices to predict global changes in spatial gene expression

2) To execute developmental perturbations in silico

DYNAMICS AND BOOLEAN SPATIAL EXRESSION

IN DEVELOPMENT, REGULATORY STATE CHANGES DYNAMICALLY IN TIME

BUT REGULATORY STATE EXPRESSION IN CELLULAR SPATIAL DOMAINS OF THE EMBRYO IS AT ANY GIVEN POINT BOOLEAN: GIVEN REGULATORY GENES ARE EITHER EXPRESSED DETECTABLY, FUNCTIONALLY ON; OR THEY ARE FUNCTIONALLY OFF.

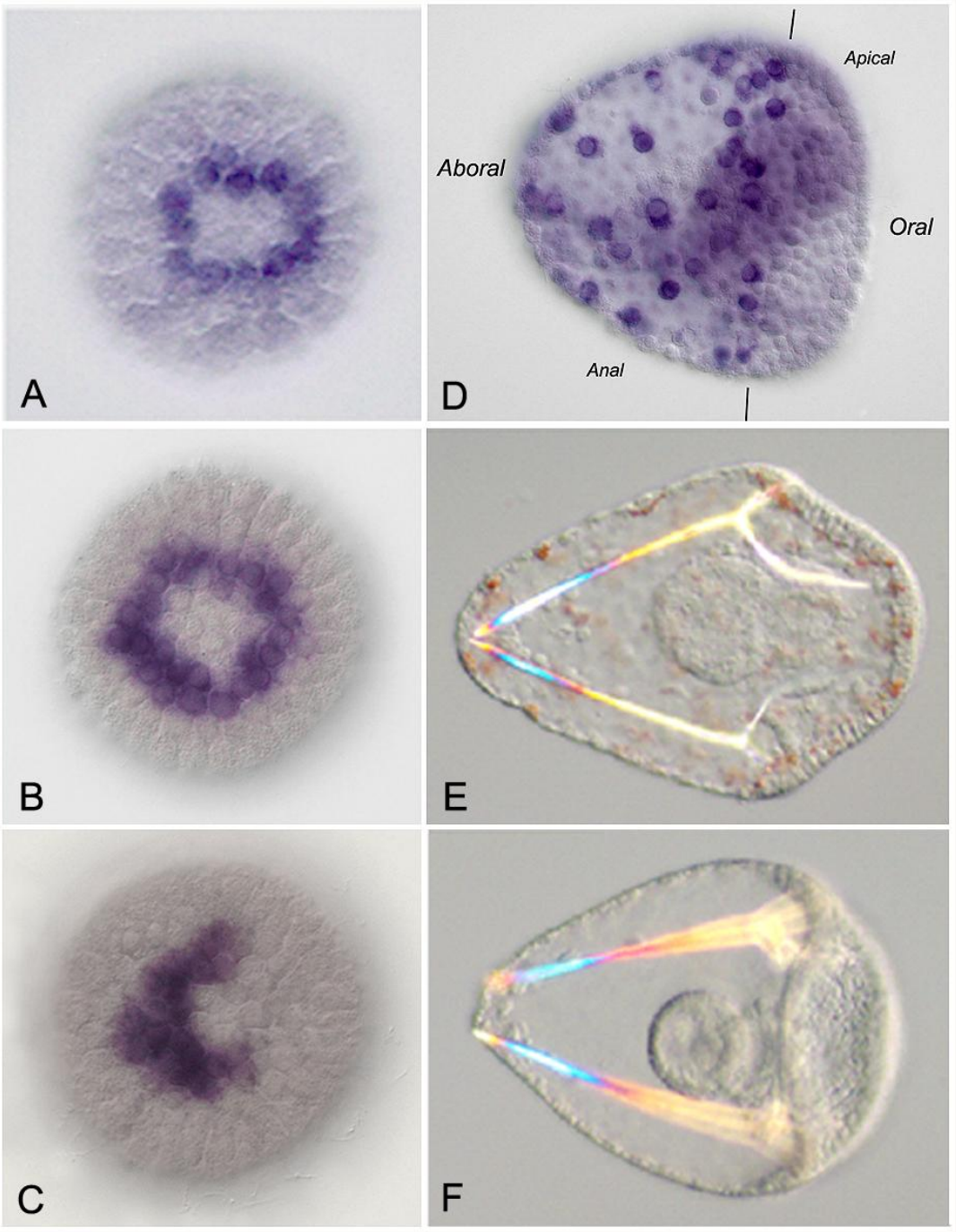
REGULATORY STATES DO NOT MERGE INTO ONE ANOTHER; THEY ARE SHARPLY BOUNDED IN ADJACENT REGIONS OF AN EMBRYO, OFTEN BY REPRESSION

gcm in situ's

12h

15h

24h



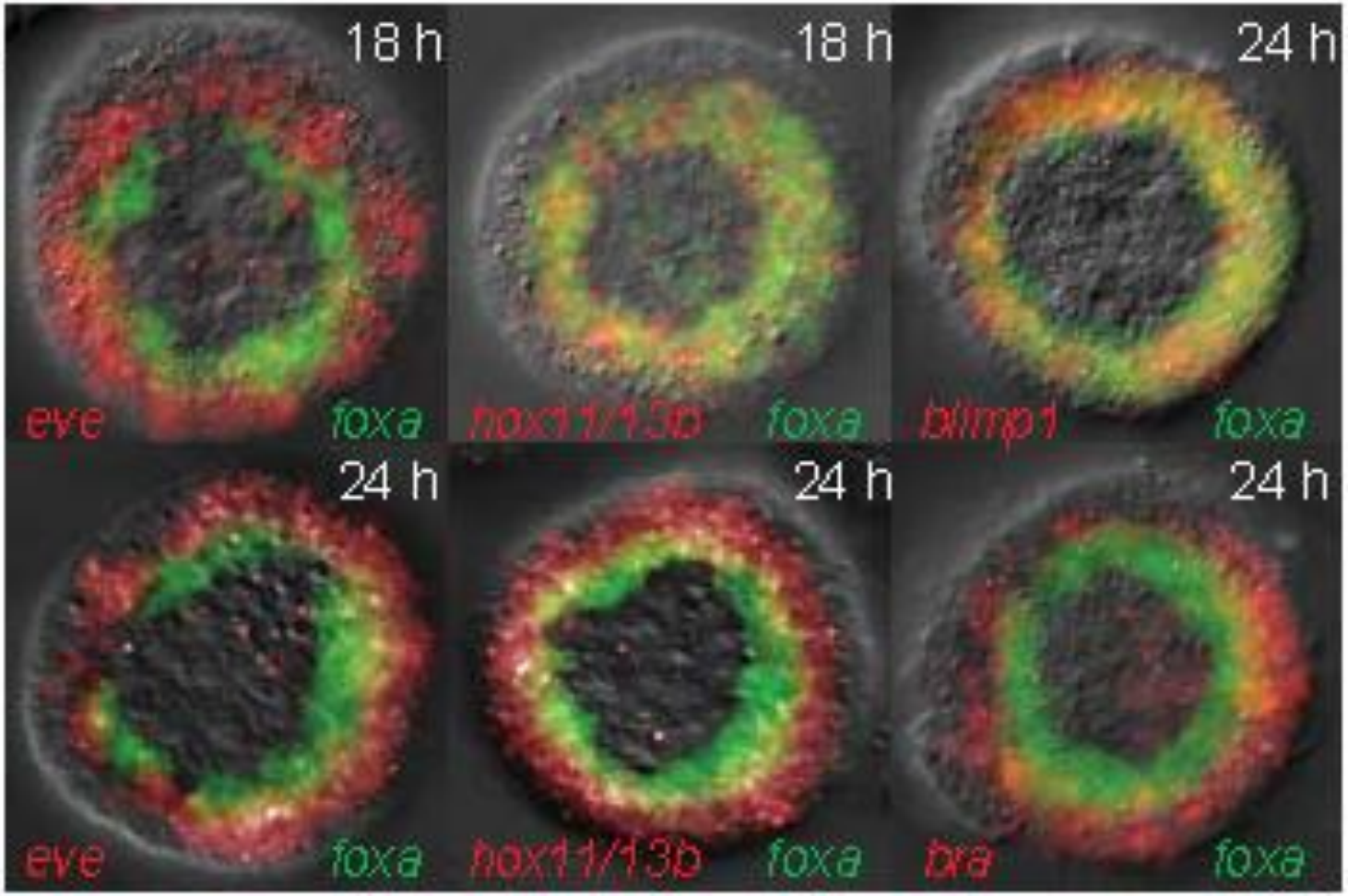
gcm in pigment cells

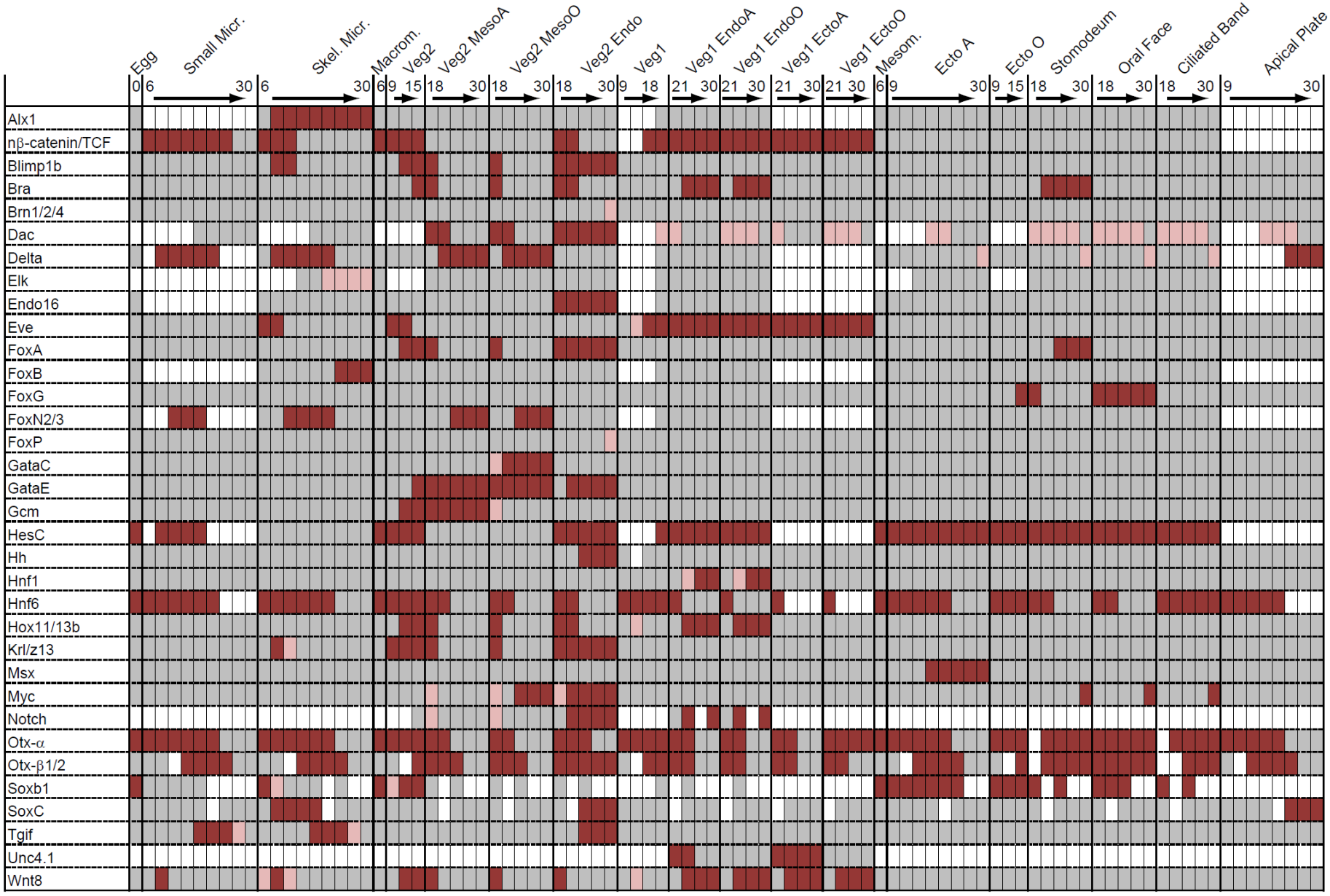
pigment cells

NO pigment cells in absence of Delta/Notch signaling

ONECUT EXPRESSION EXCLUSIVELY IN FUTURE CILIATED BAND DOMAIN

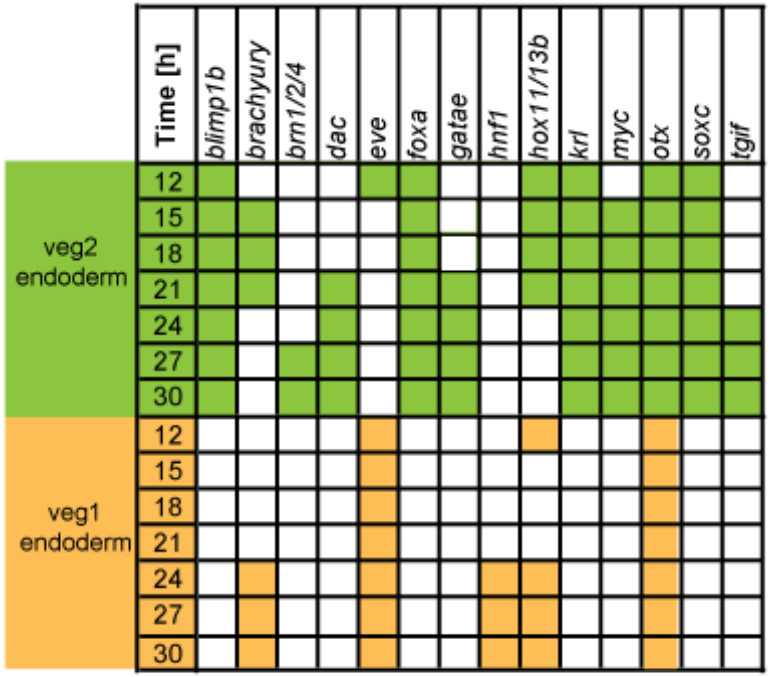
RESOLUTION TO BOOLEAN SPATIAL EXPRESSION PATTERNS




Egg
Small Micr.
Skel. Micr.
Macrom.
Veg2
Veg2 MesoA
Veg2 MesoO
Veg2 Endo
Veg1
Veg1 EndoA
Veg1 EndoO
Veg1 EctoA
Veg1 EctoO
Mesom.
Ecto A
Ecto O
Stomodeum
Oral Face
Ciliated Band
Apical Plate
0 6 30 6 30 6 9 15 18 30 18 30 18 30 9 18 21 30 21 30 21 30 21 30 6 9 30 9 15 18 30 18 30 18 30 9 30
Alx1
nβ-catenin/TCF
Blimp1b
Bra
Brn1/2/4
Dac
Delta
Elk
Endo16
Eve
FoxA
FoxB
FoxG
FoxN2/3
FoxP
GataC
GataE
Gcm
HesC
Hh
Hnf1
Hnf6
Hox11/13b
Krl/z13
Msx
Myc
Notch
Otx-α
Otx-β1/2
Soxb1
SoxC
Tgif
Unc4.1
Wnt8

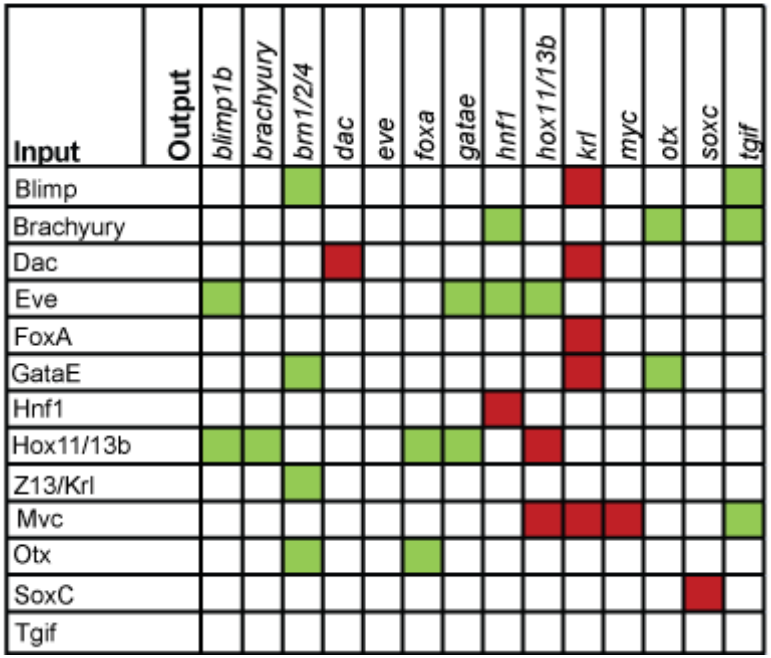
Boolean expression matrix for Veg1 and Veg2 endoderm

A



Perturbation matrix

B



Input: gene-specific morpholino knockdown
Red: increased expression
Green: decreased expression

How complete and predictive are GRN models?

Regulatory state expression is the output of GRNs

The sufficiency and completeness of a GRN model therefore has to be measured by its capacity to accurately predict the temporal and spatial transitions of regulatory states

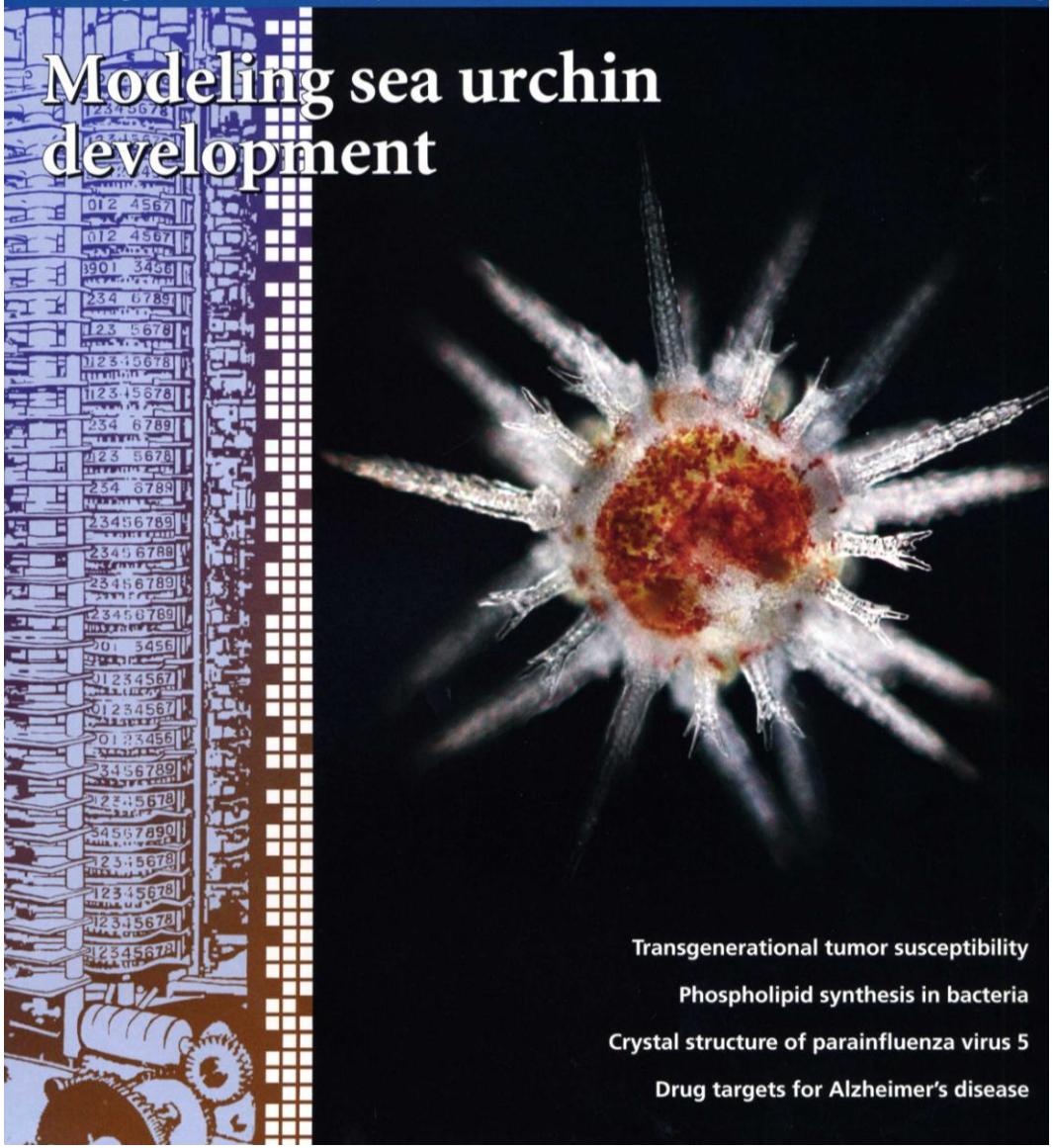
The combinatorial control of gene expression and regulatory state transitions require a computational test

October 9, 2012 | vol. 109 | no. 41 | pp. 16395–16750

PNAS

Proceedings of the National Academy of Sciences of the United States of America www.pnas.org

Modeling sea urchin development



Transgenerational tumor susceptibility

Phospholipid synthesis in bacteria

Crystal structure of parainfluenza virus 5

Drug targets for Alzheimer's disease

A NEW BOOLEAN/TEMPORAL MODEL FOR GENOMICALLY ENCODED SPATIAL GENE EXPRESSION IN THE SEA URCHIN EMBRYO

ISABELLE PETER, EMMANUEL FAURE, ERIC DAVIDSON
(PNAS 2012)

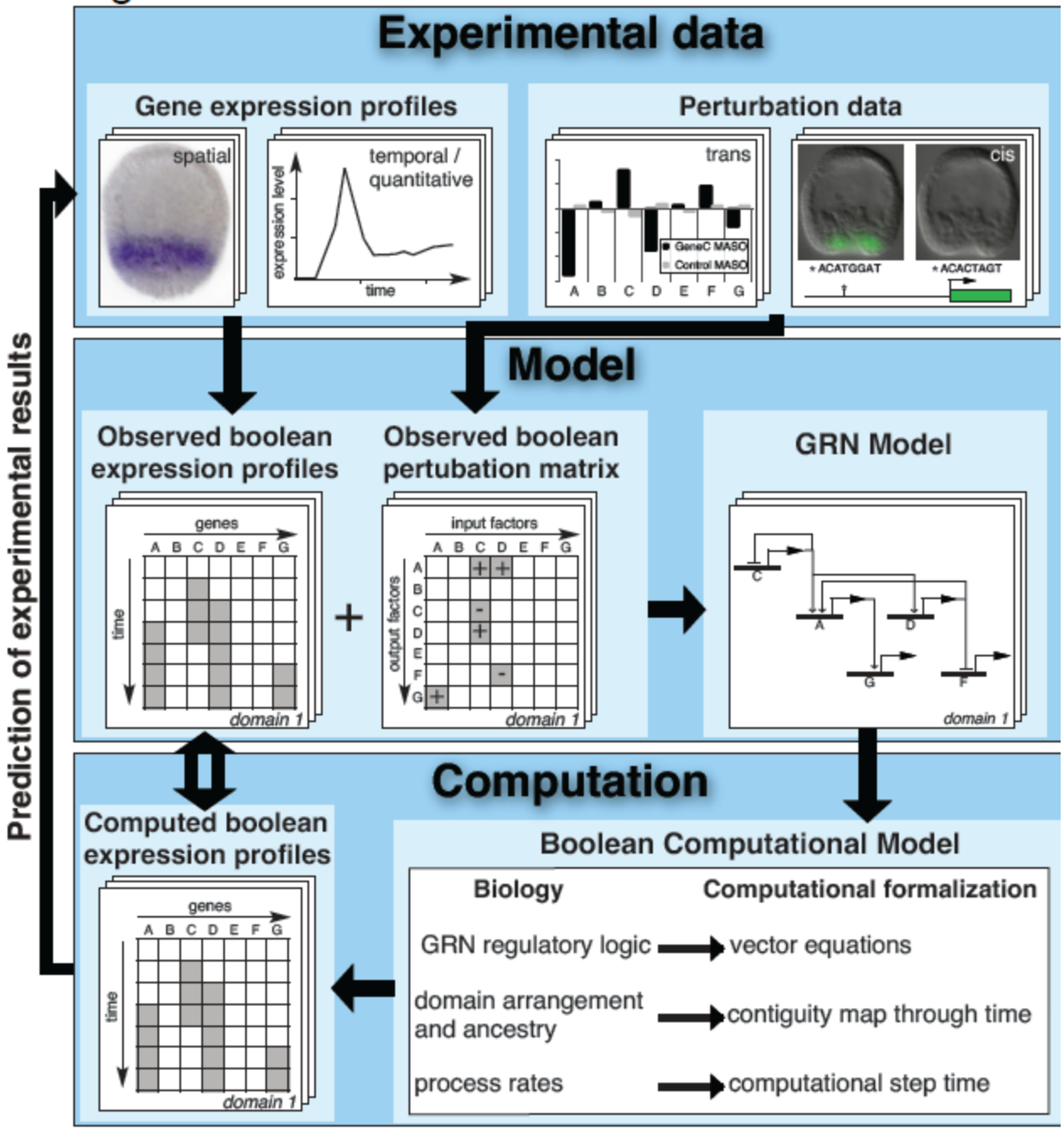
THIS MODEL CAPTURES THE GENOMIC REGULATORY LOGIC SPECIFIED IN THE GRN TOPOLOGY, AND I SHALL CLAIM :

- THAT IT PREDICTIVELY COMPUTES SPATIAL REGULATORY STATE OUTPUT ACCURATELY THROUGH TIME

- THAT IT CONFIRMS THE EXPLANATORY NEAR-SUFFICIENCY OF THE UNDERLYING GRN'S

- THAT IT ENABLES IN SILICO RE-ENGINEERING AND REGULATORY PERTURBATION ANALYSIS

Fig. 1


Experimental data
Gene expression profiles
spatial
temporal / quantitative
expression level
time
Perturbation data
trans
GeneC MASO
Control MASO
A B C D E F G
cis
+ ACATGGAT
+ ACACTAGT
Model
Observed boolean expression profiles
genes
A B C D E F G
time
domain 1
Observed boolean pertubation matrix
input factors
output factors
GRN Model
C
A
D
G
F
domain 1
Prediction of experimental results
Computation
Computed boolean expression profiles
Boolean Computational Model
Biology
Computational formalization
GRN regulatory logic
vector equations
domain arrangement and ancestry
contiguity map through time
process rates
computational step time

Principles of the Boolean model

Incorporates all linkages and all nodes of the Biotapestry GRN model (PMC, early veg2 mesoderm, veg2 and veg1 endoderm)

Every node can have the status 1 or 0 (hence Boolean) depending on the availability of its regulatory inputs

As in each nucleus, all GRN nodes are exposed to the same local regulatory state at each point in time and the model computes from this the following regulatory state at each node

Vector Equations:
Computation of regulatory interactions

"Gene A = 1
if Gene B = 1 AND Gene C = 1 AND NOT Gene D = 1,
else = 0"

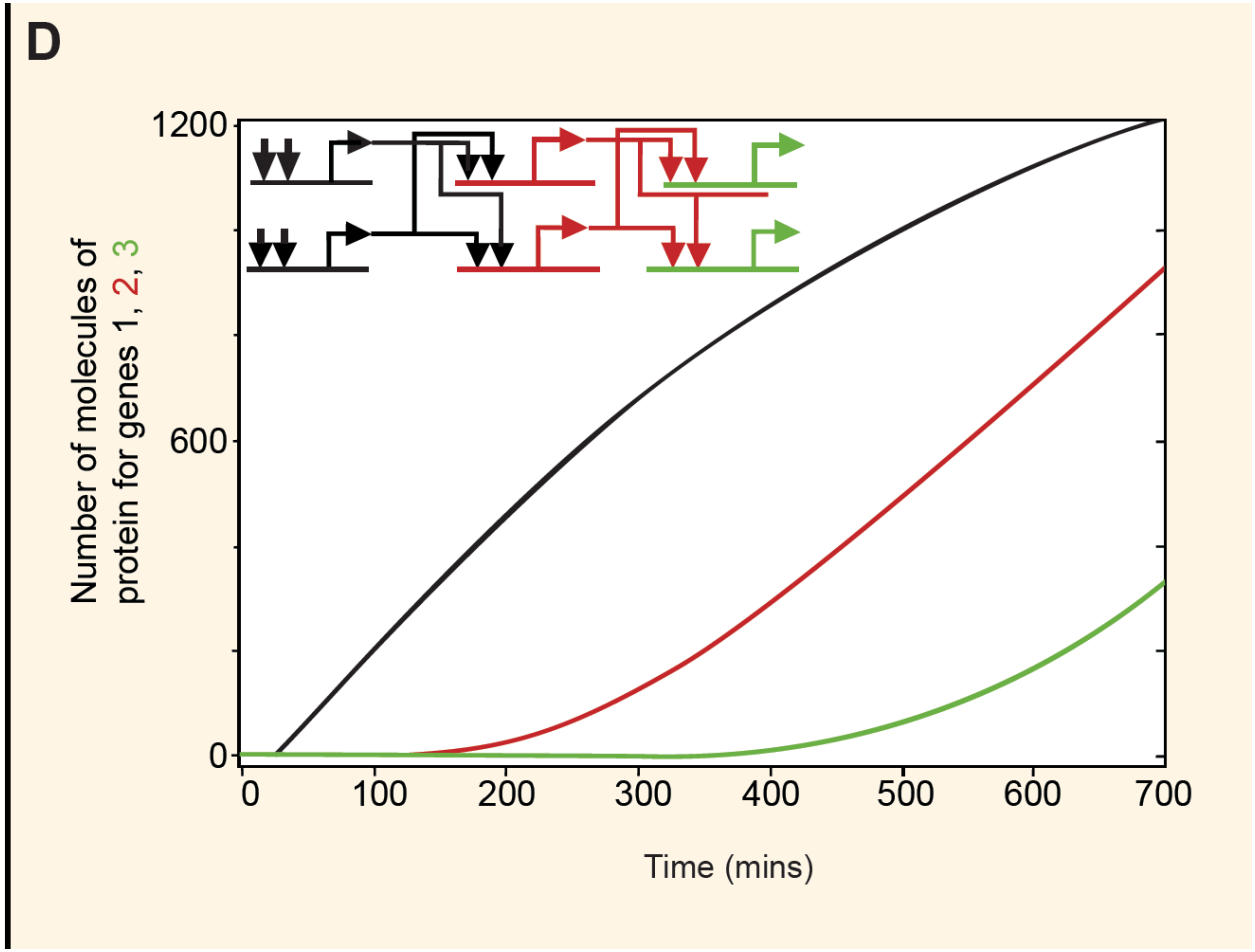
Every vector equation comes from the EXPERIMENTALLY defined GRN, based on perturbation and cis-regulatory results

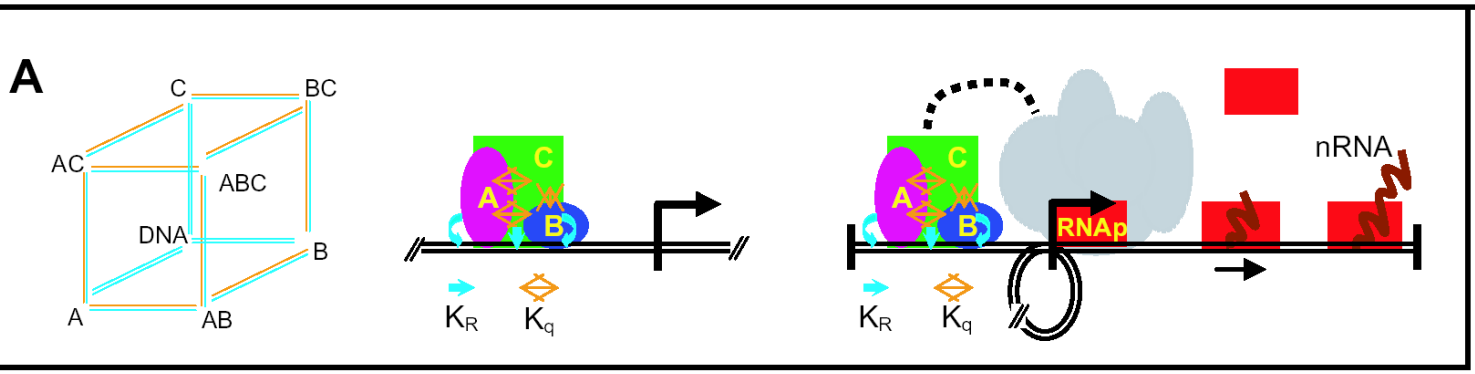
DYNAMICS

2003 KINETIC ANALYSIS: A "FIRST PRINCIPLES" MATHEMATICAL (ODE) ANALYSIS OF CIS-REGULATORY OCCUPANCY, TRANSCRIPTION, AND TRANSLATION IN WHICH GENE CASCADE DYNAMICS WERE CALCULATED USING MANY MEASURED CONSTANTS FOR SEA URCHIN EMBRYOS:

"STEP TIME": INTERVAL BETWEEN ACTIVATION OF GENE A AND OF GENE B WHERE GENE A REGULATES GENE B

IN SEA URCHIN EMBRYOS AT 15^{o} STEP TIME = ~3 H.


D
1200
600
0
Number of molecules of protein for genes 1, 2, 3
0
100
200
300
400
500
600
700
Time (mins)



$$(1) \quad Y_{AB} = \frac{A.K_{RA}.B.K_{RB}.K_q}{D_N^2 + A.D_N + B.D_N + A.K_{RA}.D_N + B.K_{RB}.D_N + A.K_{RA}.B.K_{RB}.K_q}$$

$$(2) \quad I = M.(1 - e^{-k_b.Y_{AB}/M})$$

$$(3) \quad \frac{d(nRNA)}{dt} = I - k_{dn}.nRNA$$

$$(4) \quad \frac{d(mRNA)}{dt} = I_{t+\Delta t1} - k_{dm}.mRNA$$

$$(5) \quad \frac{d(P)}{dt} = k_t.mRNA_{t+\Delta t2} - k_{dP}.P$$

K_R	= relative equilibrium constant
K_q	= coefficient of cooperativity
k_b	= CRM activating strength
Y_{AB}	= DNA occupancy by A & B
I	= no. of transcription initiations per minute
M	= max. no. of initiations per minute
$I_{t+\Delta t1}$	= initiations per minute, $\Delta t1$ mins delayed
$mRNA_{t+\Delta t2}$	= mRNA molecules, $\Delta t2$ mins after transcription
k_t	= rate of mRNA translation
k_d's	= rates of degradation

USEFUL CONCLUSIONS:

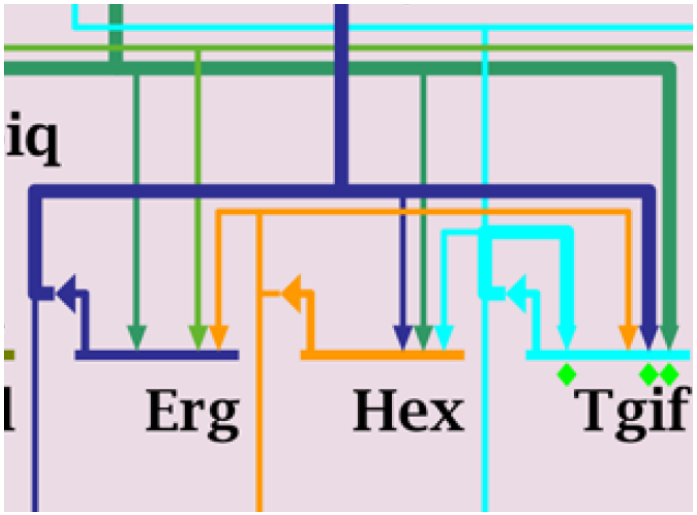
1. THE NEXT GENE IN THE CASCADE GOES ON LONG BEFORE ITS DRIVERS REACH STEADY STATE; THEREFORE SYSTEM IS LEVEL INSENSITIVE

2. THE STEP TIME IS ABOUT 3 HR (AT 15^{o})

3. NOW HAVE APPARATUS FOR CALCULATING CIRCUIT DYNAMICS

Vector Equations:
Computation of temporal dynamics

“Gene A = 1
if AT-3 Gene B = 1 AND AT-3 Gene C = 1 AND NOT
AT-2 Gene D = 1,
else = 0”



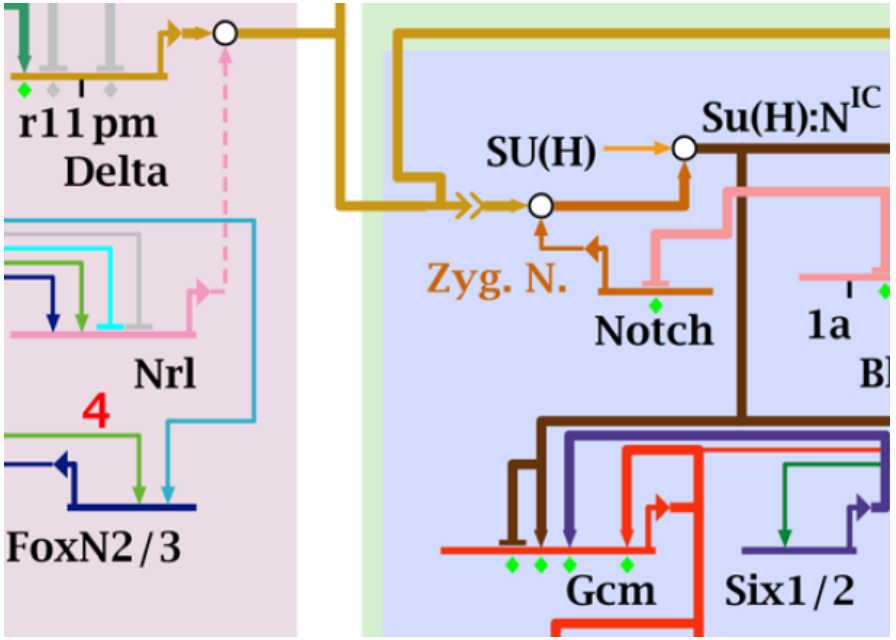
erg		if AT-3 *ets1*=1 AND AT-3 *tbr*=1 OR AT-3 *hex*=1 then=1 else=0
hex		if AT-2 *erg*=1 AND [AT-2 *ets1*=1 OR AT-2 *tgif*=1] then=1 else=0
tgif		if ModE=1 OR ModL=1 then=1 else=0
	ModE	if AT-3 *ets1*=1 AND AT-3 *hex*=1 AND AT-3 *erg*=1 then=1 else=0
	ModL	if [AT-3 *blimp1b*=1 AND AT-3 *myc*=1] AND [AT-3 *bra*=0 OR AT-3 *bra*=1] then=1 else=0

Gene		Vector Equation
alx1		if AT-2 *ets1*=1 AND AT-2 NOT *hesc*=1 then=1 else=0
blimp1b		if Mod1=1 OR Mod2=1 OR Mod3=1 then=1 else=0
	Mod1	if [AT-0 *j(tcf)*:ModH=1 OR AT-0 *j(tcf)*:ModL=1] AND PERM-0 *j(tcf)*:ModH=0 AND AT-2 *otx*=1 then=1 else=0
	Mod2	if AT-2 *hox11/13b*:ModH=1 AND AT-0 *j(tcf)*:ModH=1 AND PERM-0 *j(tcf)*:ModH=0 then=1 else=0
	Mod3	if AT-0 *j(v2)*=1 then=1 else=0
bra		if AT-3 *hox11/13b*=1 AND AT-0 *j(tcf)*=1 AND PERM-0 *j(tcf)*:ModH=0 AND AT-3 *otx*=1 AND [AT-3 *gatae*=1 OR AT-3 *gatae*=0] then=1 else=0
brn1/2/4		if AT-3 *otx*=1 AND AT-3 *blimp1b*=1 AND AT-3 *gatae*=1 AND [AT-3 *z13/krl*=1 OR AT-3 *z13/krl*=0] then=1 else=0
dac		if >17 AND IN V2 Endoderm then=1 else=0
delta		if [ModA=1 OR ModR11=1] AND AT-2 NOT *hesc*=1 then=1 else=0
	ModA	if AT-2 *runx*=1 AND AT-2 NOT *hesc*=1 then=1 else=0
	ModR11	if AT-3 *ets1*=1 then=1 else=0
dri		if AT-3 *alx1*=1 AND AT-3 *ets1*=1 then=1 else=0
erg		if AT-3 *ets1*=1 AND AT-3 *tbr*=1 OR AT-3 *hex*=1 then=1 else=0
ets1		if AT-0 *u1*=1 AND AT-2 NOT *hesc*=1 then=1 else=0
eve		if AT-2 *j(tcf)*=1 AND PERM-0 *j(tcf)*:ModH=0 AND PERM-3 [*hox11/13b*:ModH=1 AND *eve*=1] then=1 else=0
foxa		if Mod1=1 OR Mod2=1 OR Mod3=1 then=1 else=0
	Mod1	if [AT-0 *j(tcf)*:ModH=1 OR AT-0 *j(suh)*=1] AND PERM-0 *j(tcf)*:ModH=0 then=1 else=0
	Mod2	if AT-0 *j(tcf)*:ModH=1 AND AT-3 *hox11/13b*:ModH=1 AND AT-3 *otx*=1 AND [AT-3 *bra*=1 OR AT-3 *bra*=0] AND PERM-0 *j(tcf)*:ModH=0 then=1 else=0
	Mod3	if >23 AND IN V2 Endoderm then=1 else=0
foxb		if AT-3 *alx1*=1 AND AT-3 *dri*=1 AND AT-3 *ets1*=1 AND AT-3 *tbr*=1 then=1 else=0
foxn2/3		if AT-3 *tbr*=1 then=1 else=0
foxo		if AT-3 *tgif*=1 AND AT-3 *erg*=1 then=1 else=0
gatae		if [AT-3 *otx*=1 AND AT-0 *j(suh)*=1 AND AT-3 *gcm*=1] OR [AFTER-3 *hox11/13b*:ModH=1 AND AT-0 *j(v2)*=1 AND AT-3 *otx*=1] then=1 else=0
gcm		if ModE=1 OR ModG=1 then=1 else=0
	ModE	if AT-0 *j(suh)*=1 AND NOT *alx1*=1 AND PERM-0 *j(suh)*=0 then=1 else=0
	ModG	if AT-2 *gcm*=1 AND AT-2 NOT *foxa*=1 then=1 else=0
genex		if >15 AND AT-0 *j(suh)*=1 then=1 else=0
hesc		if [AT-0 *u1*=1 OR AT-0 *j(suh)*=1] AND PERM-0 *pmar1*=1 then=1 else=0
hex		if AT-2 *erg*=1 AND [AT-2 *ets1*=1 OR AT-2 *tgif*=1] then=1 else=0
hh		if AT-3 *dac*=1 AND AT-3 *foxa*=1 AND AT-3 *tgif*=1 AND AT-3 *otx*=1 AND [AT-3 *z13/krl*=1 OR AT-3 *z13/krl*=0] then=1 else=0
hnf1		if AT-2 *bra*=1 AND AT-2 *eve*=1 then=1 else=0
hox11/13b		if ModH=1 OR ModW=1 then=1 else=0
	ModH	if AT-0 *j(tcf)*:ModH=1 AND NOT [AT-3 *j(wnt16)*=1 AND AT-3 *hox11/13b*:ModH=1] AND

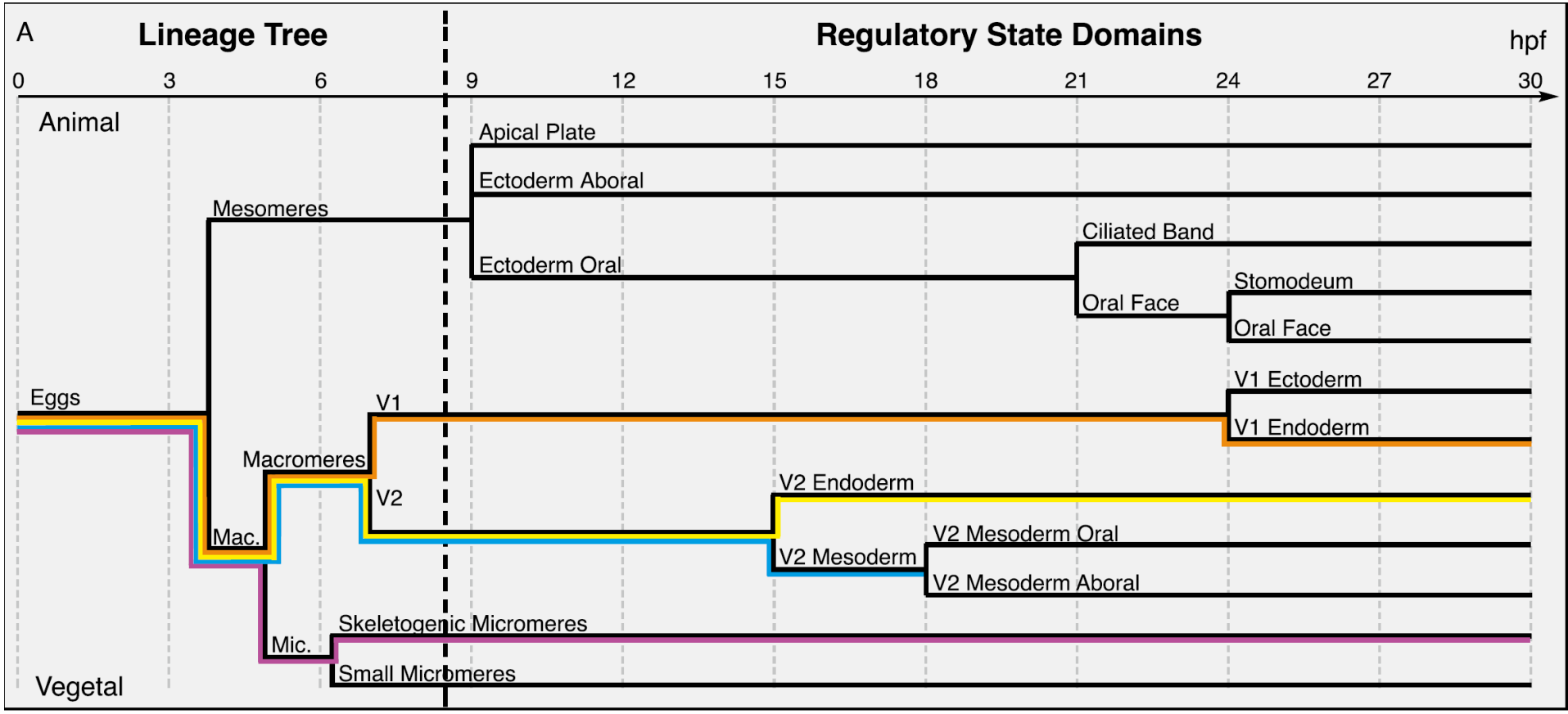
Vector Equations:
Computation of signaling interactions

"J(SuH)=1
if AT-1 delta = 1
else = 0"

"gcm=1
if AT-0 J(SuH)= 1
else = 0"



Lineage and space in the developing embryo



BASIC STRUCTURE OF MODEL:

AT EACH HR AFTER FERTILIZATION THE INPUTS AVAILABLE FROM PREVIOUS STEP (SKELETOGENIC, MESODERMAL, ANTERIOR ENDODERM, POSTERIOR ENDODERM, DOMAINS) ARE FED TO EQUATION FOR EACH GENE, IN ALL EMBRYONIC DOMAINS, AND THE OUTPUT IS COMPUTED.

CANONICAL 3HR STEP TIME IS ASSUMED FROM BOLOURI-DAVIDSON CASCADE KINETICS

MODEL OUTPUT IS A CHECKERBOARD OF COMPUTED GENE EXPRESSIONS THROUGH TIME: THIS CAN BE COMPARED DIRECTLY TO OBSERVED GENE EXPRESSION OUTPUT

:

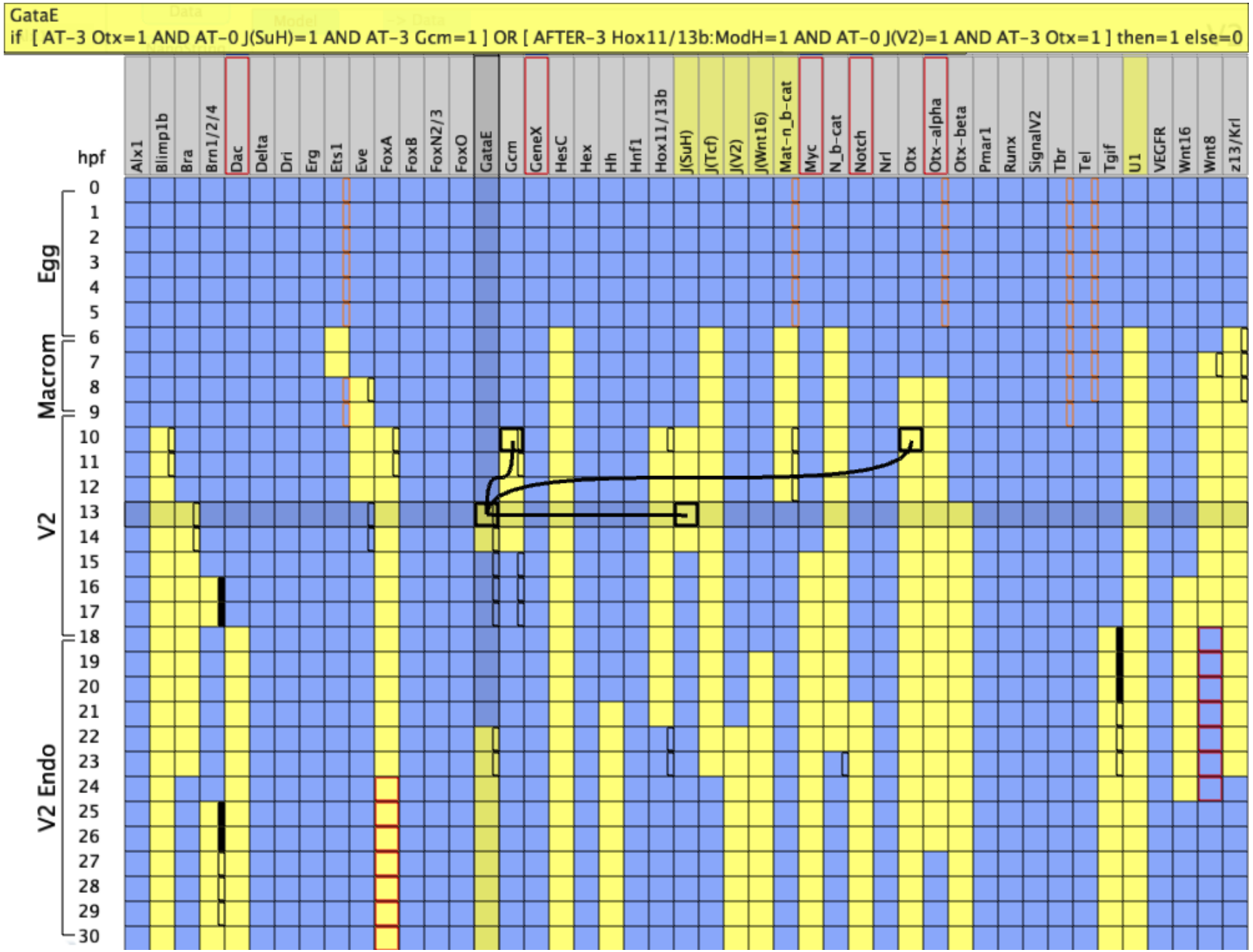
BASIC STRUCTURE OF MODEL

MODEL ENCOMPASSES CELL LINEAGE AND GEOMETRY OF EMBRYO SO CELLULAR PROXIMITY IS TAKEN INTO ACCOUNT

MODEL ENCOMPASSES MATERNAL FACTORS IN SET UP OF INITIAL STATE

MODEL HANDLES SIGNALING IN TERMS OF STATE OF IMMEDIATE EARLY TRANSCRIPTION FACTORS, WHICH DEPENDS ON WHETHER A SIGNAL IS BEING TRANSCRIBED IN ADJACENT CELLS:

E.G., J(TCF) = 1 IF CELL NEXT DOOR IS EXPRESSING THE WNT SIGNAL LIGAND, BUT= 0 OTHERWISE (WHEN TCF BECOMES A REPRESSOR)


GataE
if [AT-3 Otx=1 AND AT-0 J(SuH)=1 AND AT-3 Gcm=1] OR [AFTER-3 Hox11/13b:ModH=1 AND AT-0 J(V2)=1 AND AT-3 Otx=1] then=1 else=0
hpf
Egg
Macrom
V2
V2 Endo
Alx1
Blimp1b
Bra
Brn1/2/4
Dac
Delta
Dri
Erg
Ets1
Eve
FoxA
FoxB
FoxN2/3
FoxO
GataE
Gcm
GeneX
HesC
Hex
Hh
Hnf1
Hox11/13b
J(SuH)
J(Tcf)
J(V2)
J(Wnt16)
Mat-n_b-cat
Myc
N_b-cat
Notch
Nrl
Otx
Otx-alpha
Otx-beta
Pmar1
Runx
SignalV2
Tbr
Tel
Tgif
U1
VEGFR
Wnt16
Wnt8
z13/Krl
0
1
2
3
4
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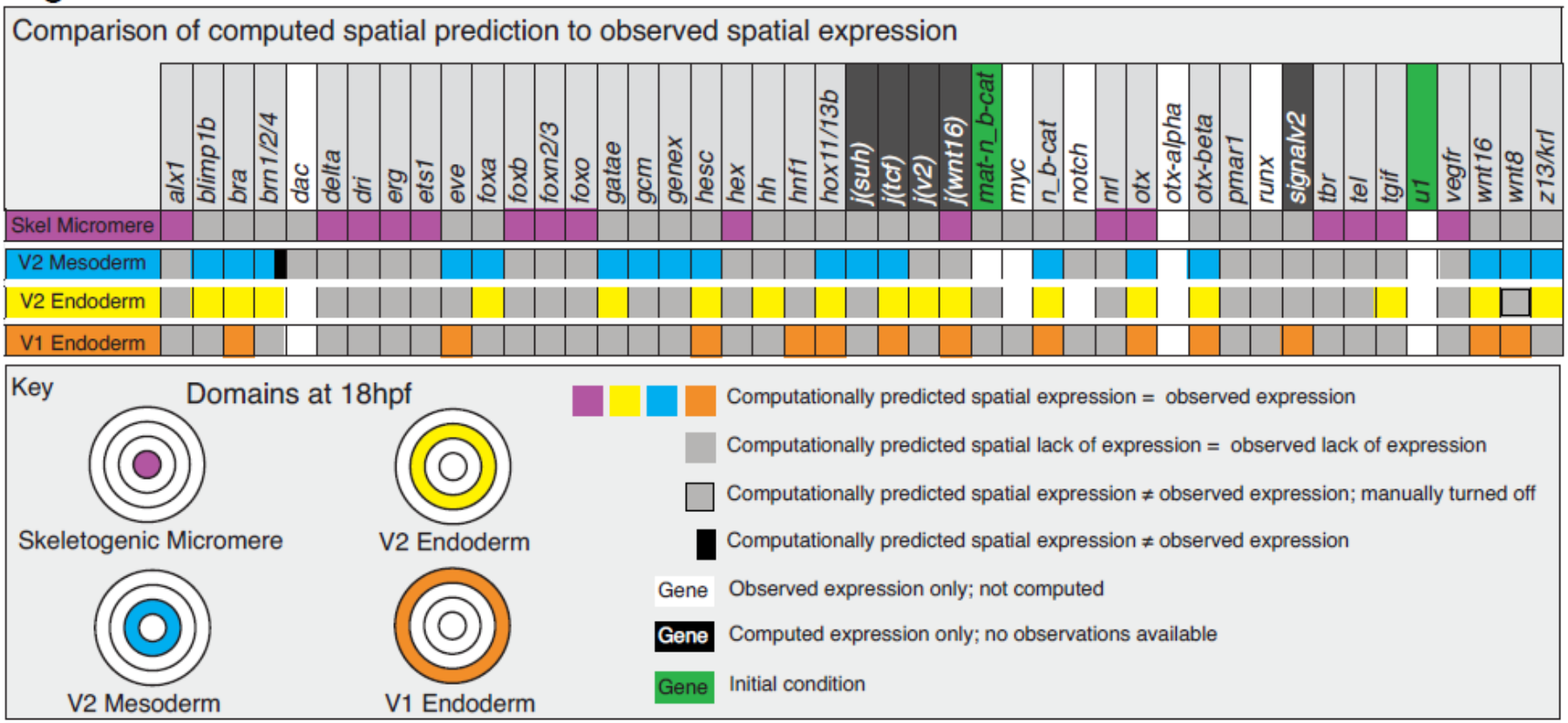
RESULTS

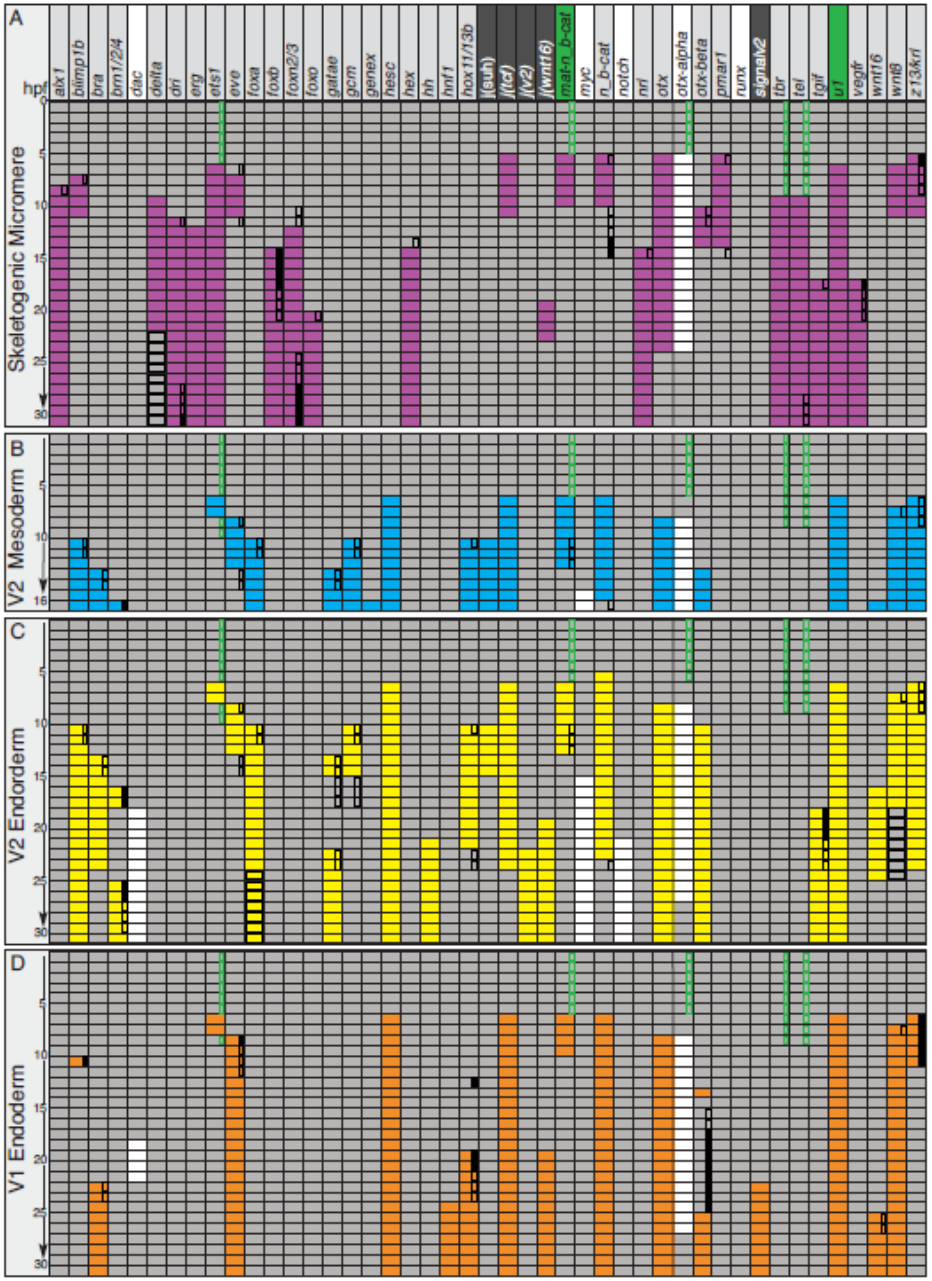
COMPUTED SPATIAL REGULATORY STATES 18-30H VS. DATA: 13O/132 [GENE-DOMAINS] CORRECTLY PREDICTED

Fig. 2



COMPUTATION OF HOURLY SPATIAL EXPRESSION vs DATA: OUT OF 2772 SPACE/TIME EXPRESSION DOMAINS VERY FEW SIGNIFICANT DISCREPANCIES…

Fig. 3



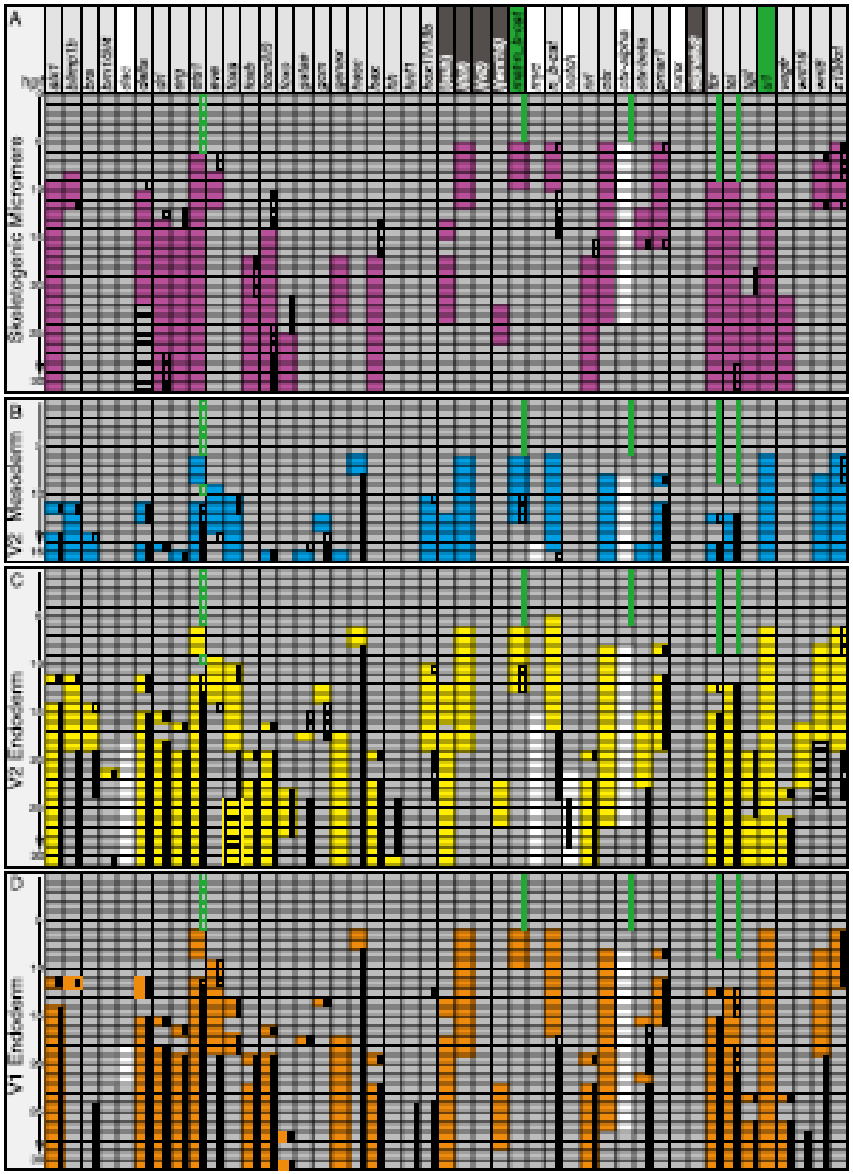


Fig. S7. Effect on model performance of altering the step time to 4 h. Step times were altered in all vector equations from 3 h to 4 h. The form of the figure is the same as that of Fig. 3, showing the four spatial domains (A–D). Comparison with Fig. 3 illustrates the dramatic increase in severe deviations from the observed expression data caused by alteration of step time, demonstrating the importance of an accurate estimation of the step time.

MERELY CHANGING STEP TIME TO 4 HR TOTALLY RUINS FIDELITY OF COMPUTATION

IN SILICO PERTURBATIONS VS. EXPERIMENTAL RESULTS

1. BLOCKADE OF SKELETOGENIC MICROMERE DELTA EXPRESSION (EXPERIMENTAL RESULT: STOPS MESODERMAL SPECIFICATION; FAILURE OF ENDODERM EXTINCTION IN INNER VEG2 RING)

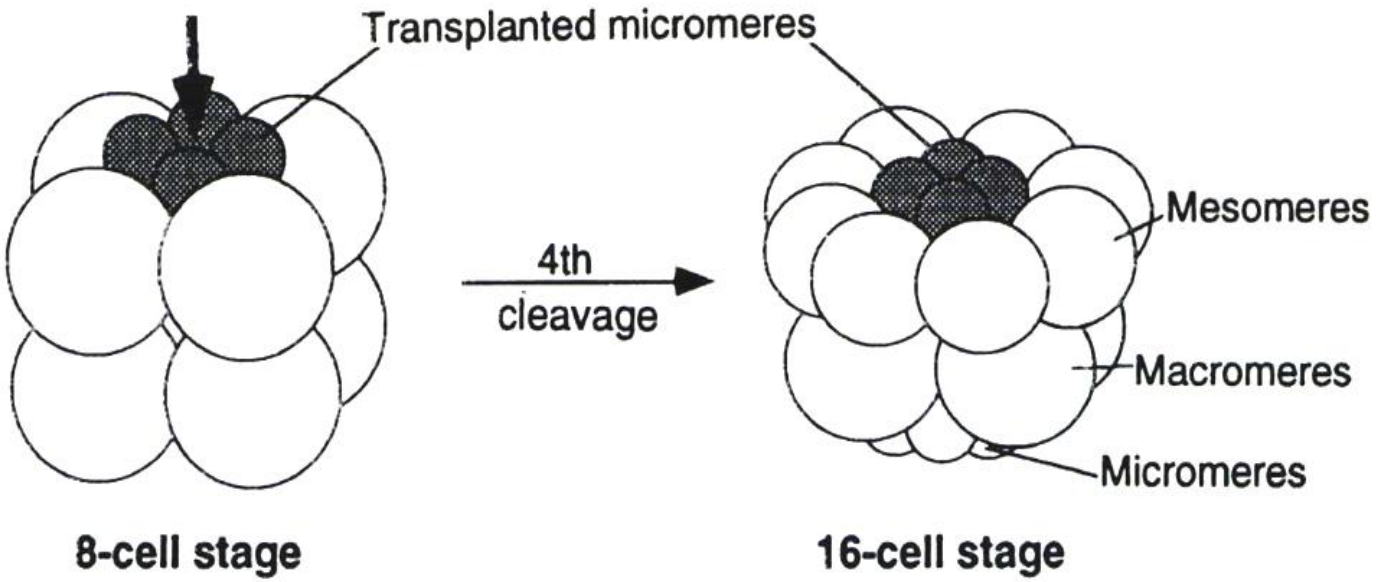
2. GLOBAL EXRESSION OF PMAR1 (RESULT: TURNS WHOLE EMBRYO INTO MESENCHYME)

3. TRANSPLANTATION OF MICROMERES TO TOP OF EMBRYO (RESULT: ESTABLISHMENT OF ECTOPIC MESODERM, ANTERIOR ENDODERM AND POSTERIOR ENDODERM; COMPLETE SECOND ENDOMESODERM)

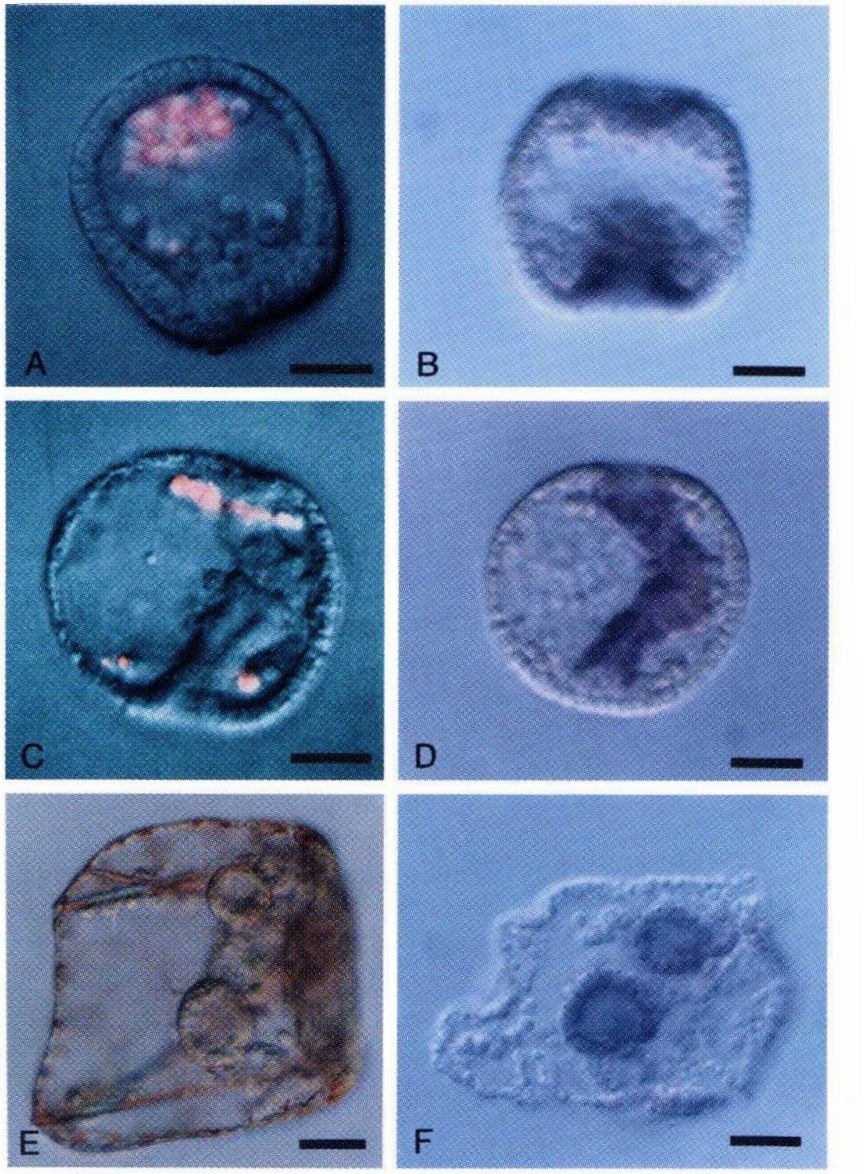
IN 1935 SVEN HORSTADIUS TRANSPLANTED MICROMERES TO ANIMAL POLE AND DEMONSTRATED INDUCTION OF COMPLETE SECOND GUT AT TOP OF SEA URCHIN EGG

IN 1993 RANSICK & DAVIDSON REPEATED THIS USING MOLECULAR MARKERS AND SHOWED WHOLE OF PROPERLY PATTERNED ENDOMESODERM IS INDUCED AT TOP OF EGG

DOES THE GRN MODEL CONTAIN SUFFICIENT INFORMATION TO OBTAIN THIS RESULT IN SILICO AND GENERATE REQUIRED REGULATORY STATES ECTOPICALLY IN NAÏVE CELLS??

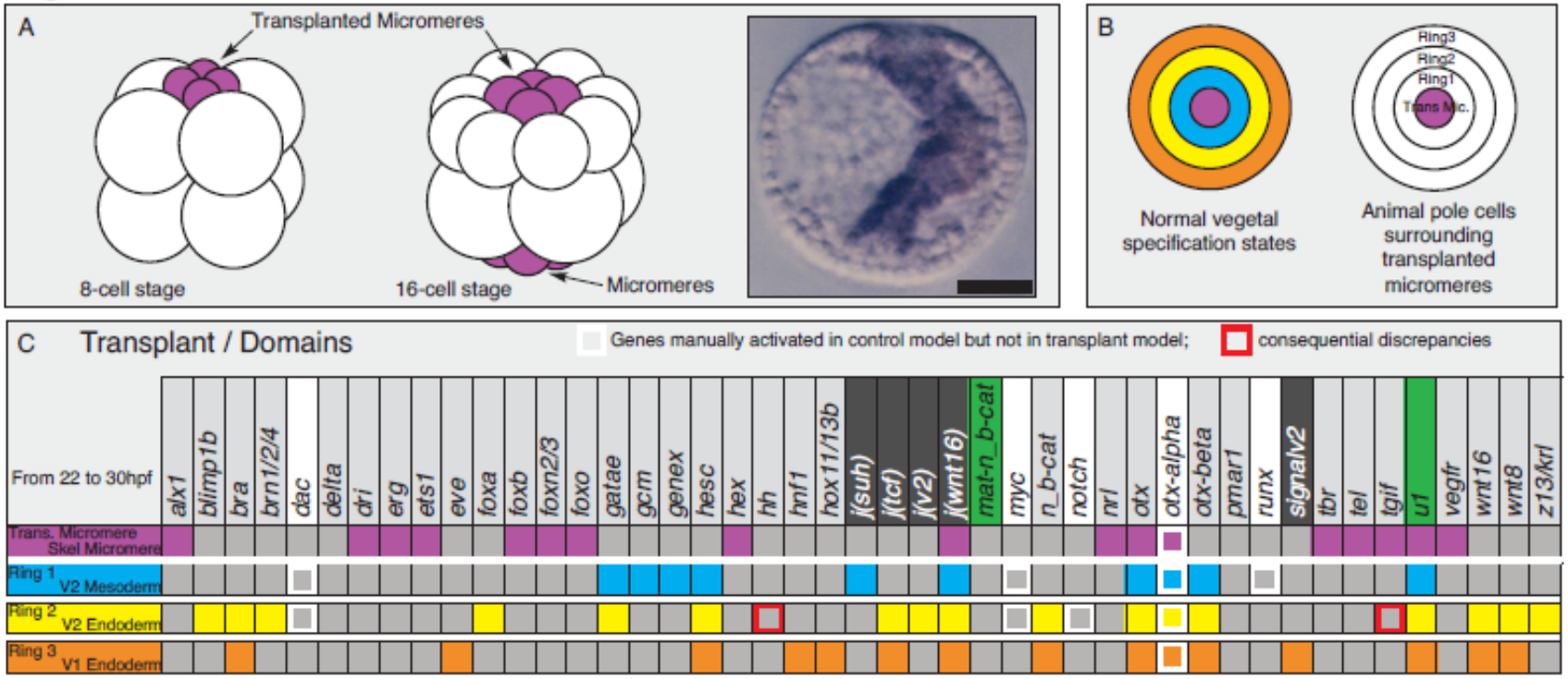

Transplanted micromeres
4th
cleavage
Mesomeres
Macromeres
Micromeres
8-cell stage
16-cell stage

RANSICK, DAVIDSON 1993



HORSTADIUS 1935 MICROMERE TRANSPLANTATION EXPERIMENT PERFORMED IN SILICO: DOES THE MODEL CONTAIN SUFFICIENT INFORMATION TO GENERATE REQIRED REGULATORY STATES ECTOPICALLY IN NAÏVE CELLS??

Fig. 5



Computed perturbation result vs. gene expression in normal equivalent territory

SOME CONCLUSIONS-1

THE GRN'S HAVE SUFFICIENT GENOMICALLY ENCODED INTERACTION INFORMATION TO PROVIDE AN ALMOST COMPLETE, PROGRESSIVE, COMPUTATION OF REGULATORY STATE IN TIME AND SPACE

WHAT WE DON'T YET KNOW IS SPECIFICALLY HIGHLIGHTED, WHICH IS VERY USEFUL

BUT INSTEAD OF A FEW ISLANDS OF CAUSALITY FLOATING IN A SEA OF PHENOMENOLOGY, WE NOW HAVE A FEW ISLANDS OF PHENOMENOLOGY EMBEDDED IN A CAUSAL SYSTEM-LEVEL FRAMEWORK

SOME CONCLUSIONS-2

WITH RESPECT TO SPATIAL/TEMPORAL, ON/OFF GENE EXPRESSION, FOR THIS EARLY EMBRYO THERE IS NOT MUCH ROOM FOR OTHER LEVELS OF EXPLANATION (EPIGENETICS, MI-RNA'S)

(THESE ADDITIONAL LAYERS OF REGULATION MAY BE MORE IMPORTANT IN LATER DEVELOPMENT)

THUS, IN THE EMBRYO, CONTROL OF REGULATORY STATE IN SPACE AND TIME DEPENDS DIRECTLY ON GENOMICALLY ENCODED, SEQUENCE–DEPENDENT REGULATORY INTERACTIONS

SOME CONCLUSIONS-3

GIVEN AN EXPERIMENTALLY WELL-VALIDATED GRN MODEL:

--DOWNSTREAM CONSEQUENCES OF TRANS-PERTURBATIONS CAN BE COMPUTATIONALLY PREDICTED

--RE-ENGINEERING AT THE CIS-REGULATORY LEVEL CAN BE DONE BY CHANGING VECTOR EQUATIONS, AND THE CONSEQUENCES DETERMINED IN SILICO ON A SYSTEM WIDE SCALE

--THUS EVOLUTIONARY PROCESSES THAT AFFECT DEVELOPMENT CAN BE MODELED REALISTICALLY IN SILICO

--THIS OPENS THE WAY TO A RATIONAL, SYNTHETIC LABORATORY APPROACH TO UNDERSTANDING EVOLUTION

A FUNDAMENTAL QUESTION IN DEVELOPMENTAL CONTROL THEORY: HOW CAN CONTINUOSLY VARYING, MICROSCOPICALLY NOISY, MOLECULAR PROCESSES PRODUCE REPRODUCIBLE, SHARP, BOOLEAN SPATIAL EXPRESSION OUTCOMES?????

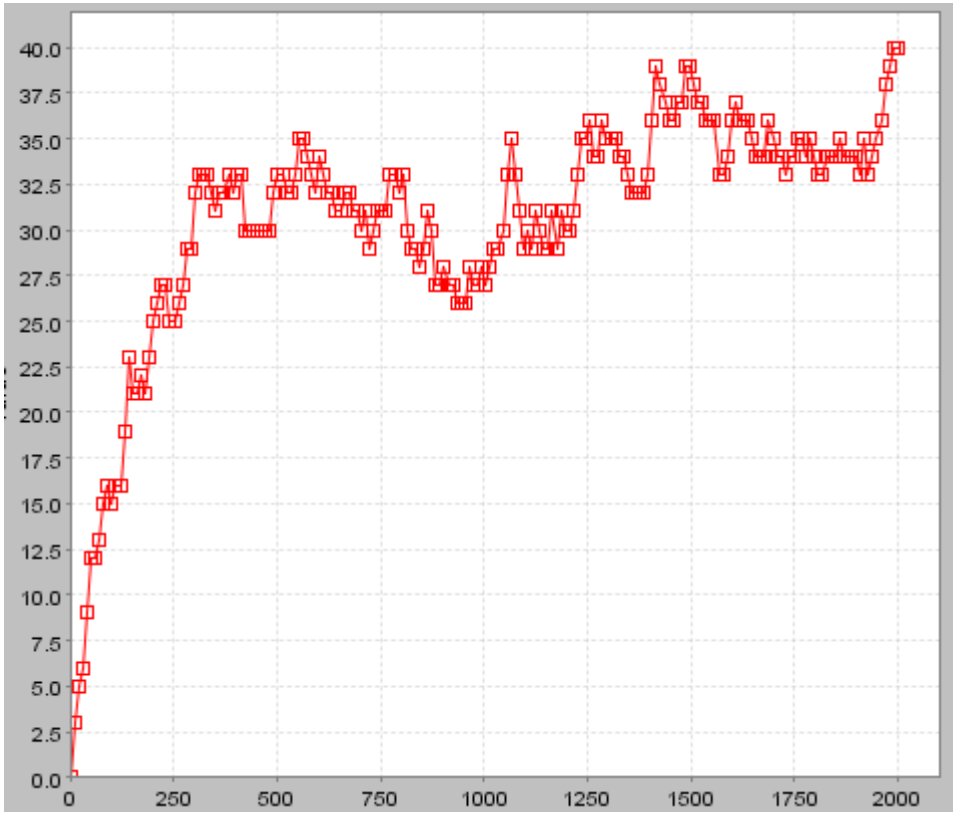
GENERAL ANSWERS:

-INSENSITIVITY OF EMBRYONIC TRANSCRIPTIONAL EXPRESSION TO INPUT FACTOR LEVEL VARIATIONS

-GRN CIRCUITRY BUFFERS VARIATION IN MANY WAYS

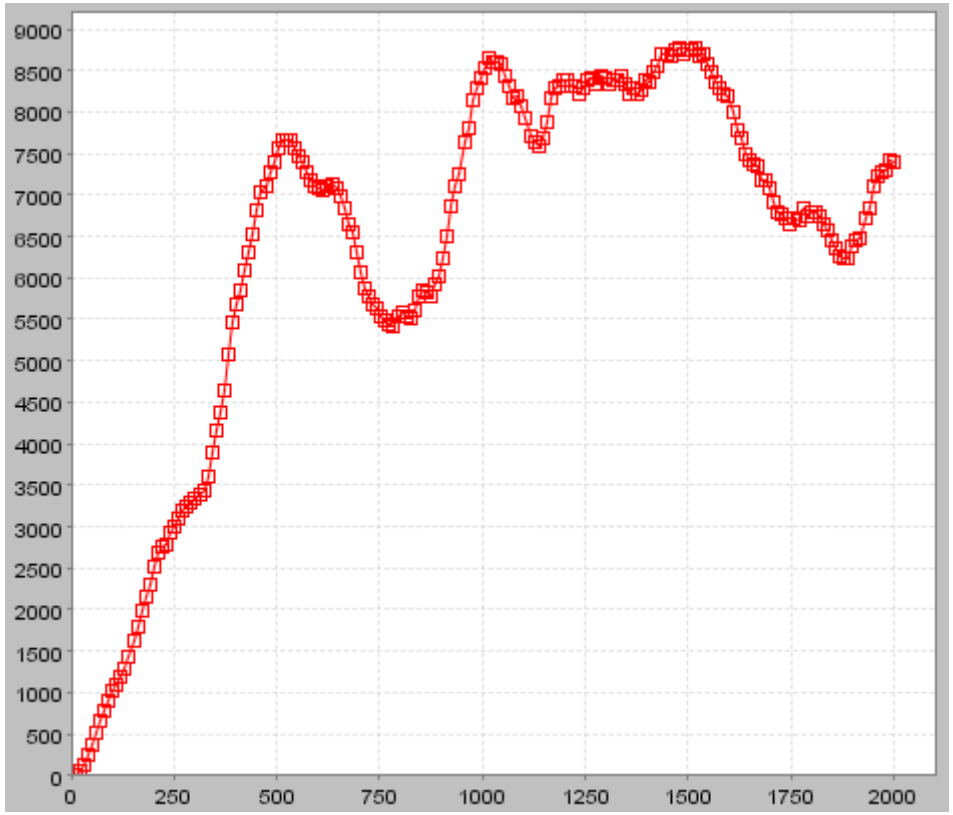
-DOMINANT MULTISTEP NATURE OF REPRESSION

mRNA molecules in a single cell



Time (minutes after activation)

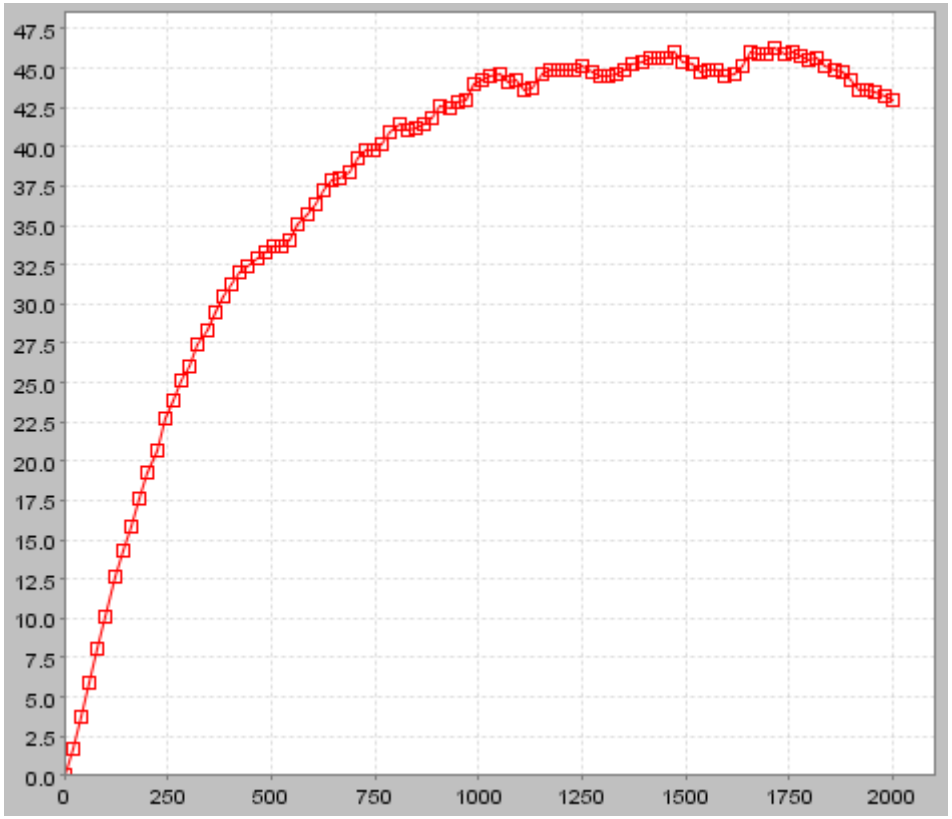
protein molecules in a single cell



Time (minutes after activation)

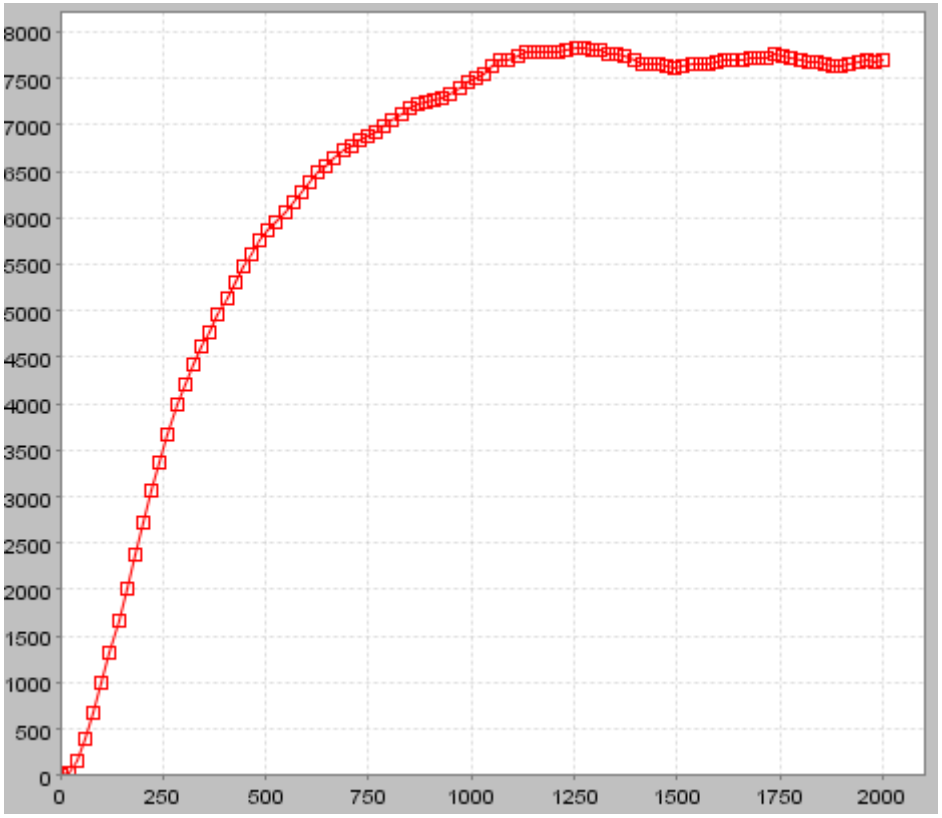
STOCHASTIC TRANSCRIPTION/TRANSLATION SIMULATION FOR SINGLE CELL, SEA URCHIN PARAMETERS : VARIATION <30% MAX

Number of mRNA molecules per cell averaged over 50 cells



Time (minutes after activation)

Number of protein molecules per cell averaged over 50 cells



Time (minutes after activation)

STOCHASTIC TRANSCRIPTION/TRANSLATION SIMULATION FOR OUTPUT OF FIELD OF 50 EQUALLY STOCHASTIC CELLS

BUFFERING OF UPSTREAM VARIATION BY GRN CIRCUITRY

-REPRESSION CIRCUITS BETWEEN CELLS OF DIFFERENT SPATIAL DOMAINS

-FEEDBACK CIRCUITS WITHIN CELLS

-COMMUNITY EFFECT CIRCUITS AMONG CELLS OF GIVEN SPATIAL DOMAINS

THE PEOPLE WHO MAKE THE DISCOVERIES

For this talk:

- **EMMANUEL FAURE: Boolean logic model; computational virtual embryo**
- **QIANG TU: Feedback circuitry in skeletogenic GRN; embryonic, adult tissue and genomic transcriptome analysis**
- **ANDY RANSICK: Gcm cis-reg, N signaling pathway, the double gut experiment**
- **FENG GAO: Hijacking skeletogenesis; Cis-reg basis of cooption;The sox21 project**
- **ENHU LI: The new Oral/Aboral Ectoderm GRNs**
- **JULIUS BARSI: The ciliated band GRN; the Global Network Project**
- **STEFAN MATERNA: Expanding the Mesoderm GRN; Individual transcript levels**
- **ANDY CAMERON: The S. purpuratus GENOME CENTER and database; brachyury cis-reg; cis-reg module evolution; BI COMPUTATIONAL CENTER FOR REGULATORY GENOMICS**
- **ERIC ERKENBRACK: Eucidaris developmental GRN**
- **JON VALENCIA: Later endoderm cis-reg project**
- **BILL LONGABAUGH: Computational collaboration on BioTapestry development**
- **DOUG ERWIN; DAVID BOTTJER; JL SKARMETA ET. AL: Important collaborators**

- **SUPPORT: NICHD; also, NIGMS, NCRR, NSF, Beckman Institute; HGRI, Richard Gibbs, & the Baylor HGSC**