FORMAL METHODS IN CELL BIOLOGY

Jasmin Fisher

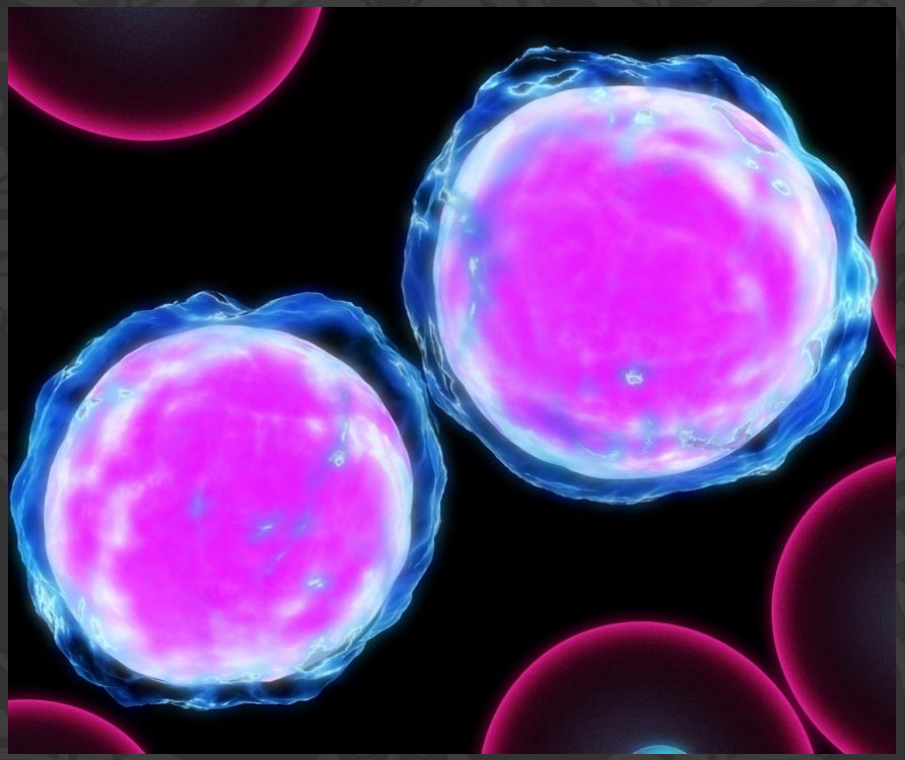
Microsoft Research Cambridge

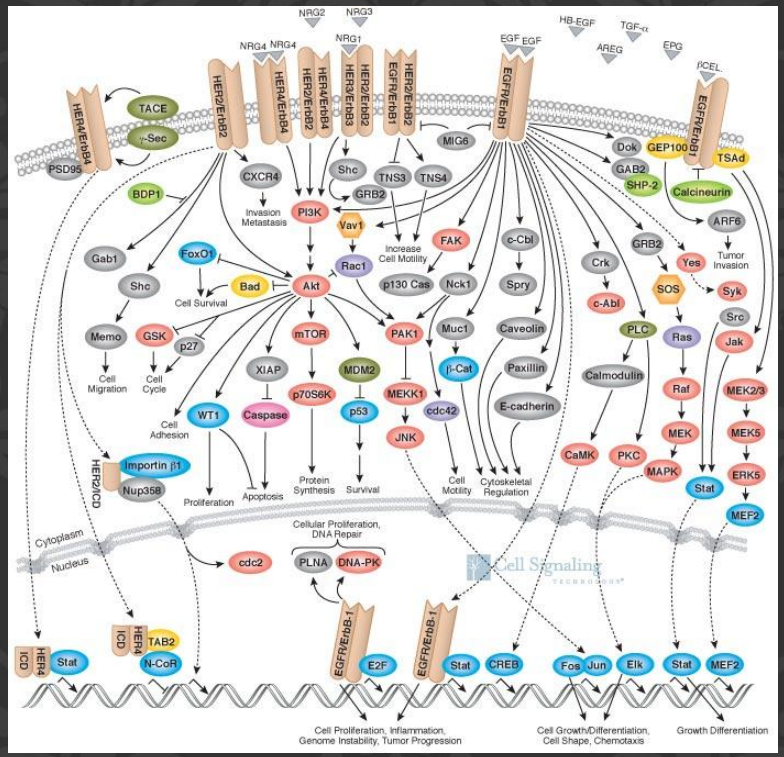
Tutorial, FMCAD 2012

Cambridge, UK

Executable Biology

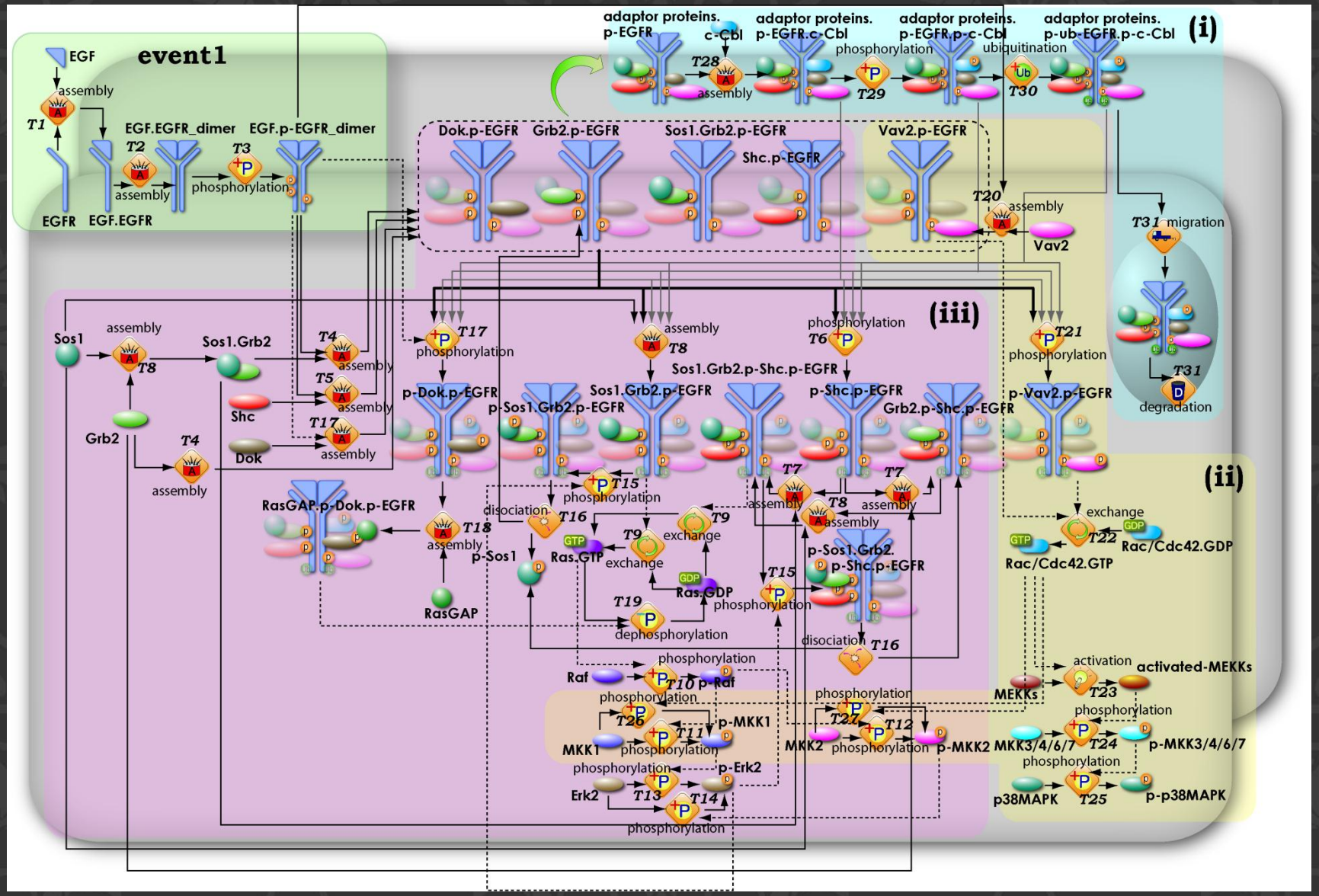
Tackling the problem of complexity



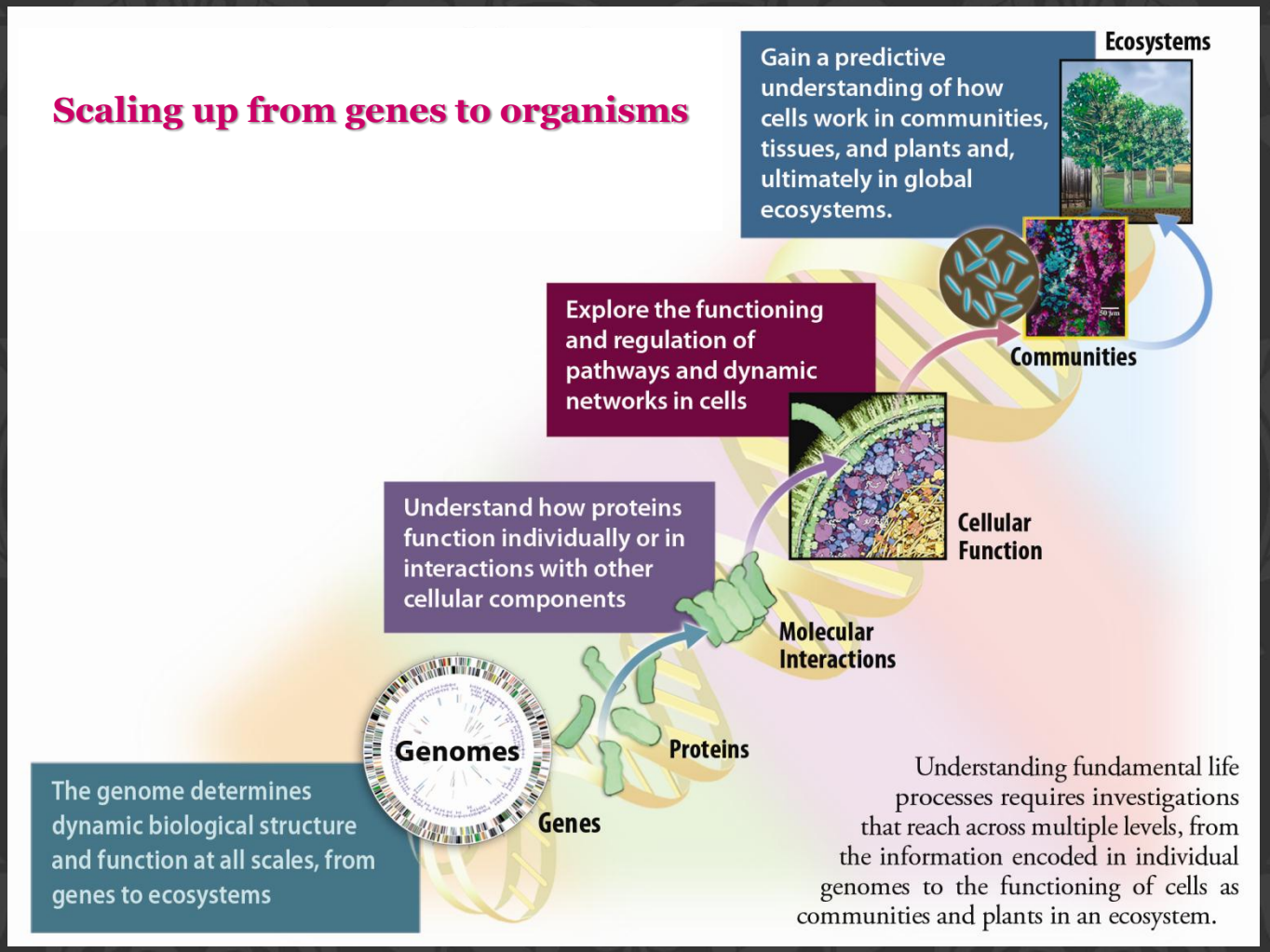


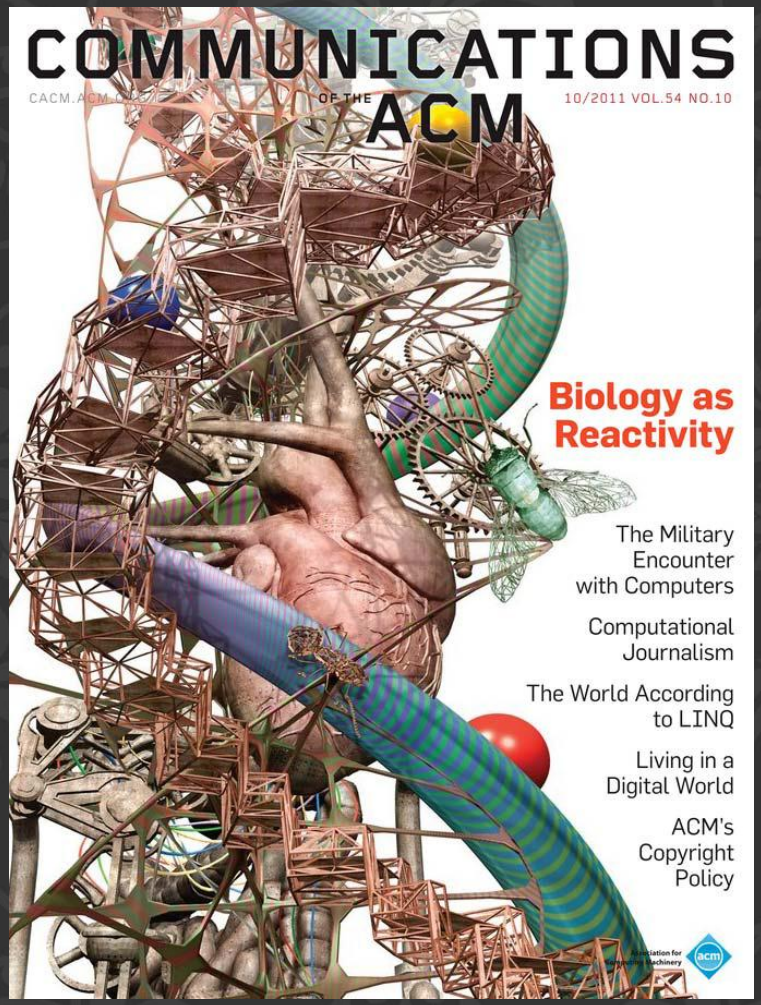
Biocomplexity

e.g. EGFR signalling pathway



Scaling up…


Scaling up from genes to organisms
Gain a predictive understanding of how cells work in communities, tissues, and plants and, ultimately in global ecosystems.
Ecosystems
Explore the functioning and regulation of pathways and dynamic networks in cells
Communities
Understand how proteins function individually or in interactions with other cellular components
Cellular Function
Molecular Interactions
Genomes
Proteins
Genes
The genome determines dynamic biological structure and function at all scales, from genes to ecosystems
Understanding fundamental life processes requires investigations that reach across multiple levels, from the information encoded in individual genomes to the functioning of cells as communities and plants in an ecosystem.



Fisher, Harel & Henzinger *CACM* (2011)

Systems Biology

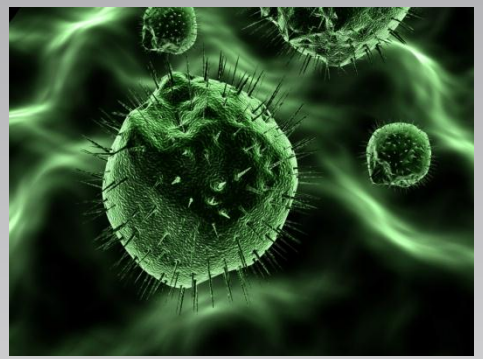
- **System** level understanding of living systems.
- Establish the methodologies and techniques to understand biological complexity.

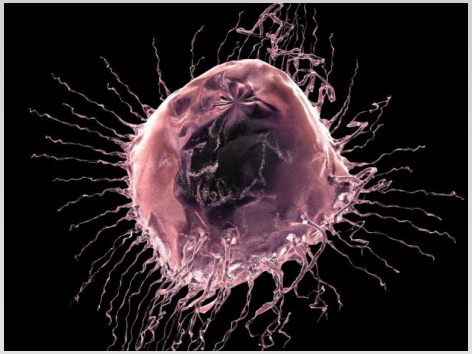
From data collection to data analysis…

- Data mining
- Classical bioinformatics (omics…)
- Synthetic Biology
- Executable Biology

Engineering

Reverse - Engineering





Use of formal methods to model biological systems

A tale of two cultures…

A Mathematical models

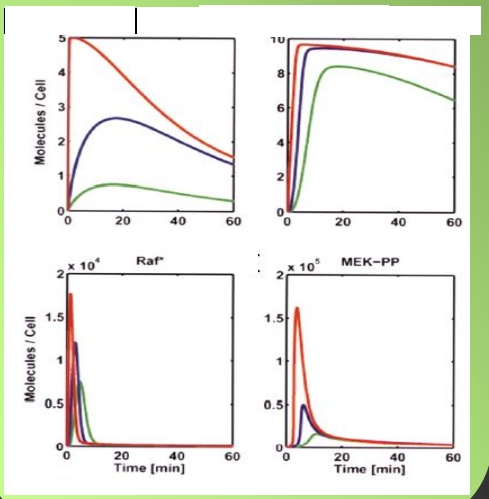
$$\frac{d[c_1]}{dt} = 3.84\times10^{-3}\times c_3 - 3.00E\times10^{7}\times c_1\times c_2$$

$$\frac{d[c_2]}{dt} = \begin{array}{c} 3.84\times10^{-3}\times c_3 + 5.00\times10^{-4}\times c_8 + \\ -3.00\times10^{7}\times c_3 - 5.00\times10^{-3}\times c_8 \end{array}$$

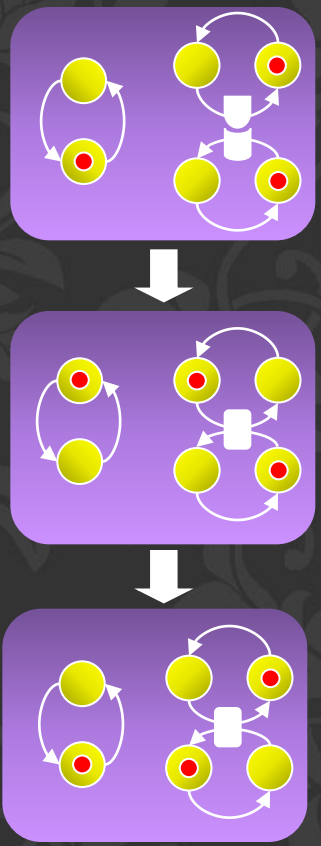
$$\frac{d[c_3]}{dt} = 3.00\times10^{7}\times c_1\times c_2 - 3.84\times10^{-3}\times c_3$$

$$\frac{d[c_8]}{dt} = 1.73\times10^{-7}\times c_5\times c_6 - 0.2\times c_8$$

$$\frac{d[c_5]}{dt} = 1.46\times10^{-2}\times c_3 - 1.66\times10^{-6}\times c_5$$



B Computational models



Fisher J. & Henzinger T.A. *Nature Biotechnology* (2007) **25**(11):1239-1249

Mathematical vs. Computational Models

Mathematical

Denotational semantics

Equations describing the relations between quantities and change over time.

Equations do not prescribe an algorithm for solving them.

Computational

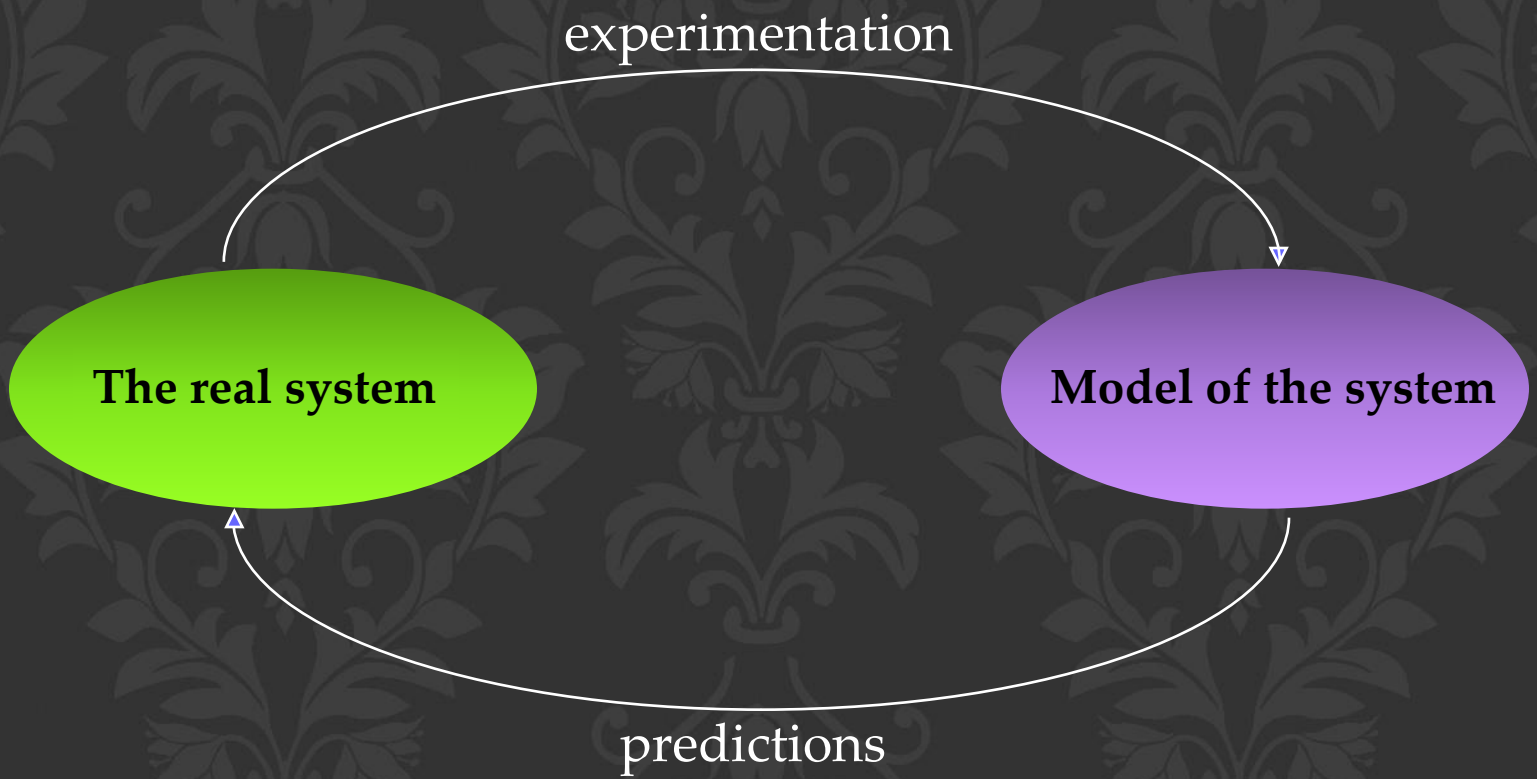
Operational semantics

Sequence of steps to be taken by abstract machine.

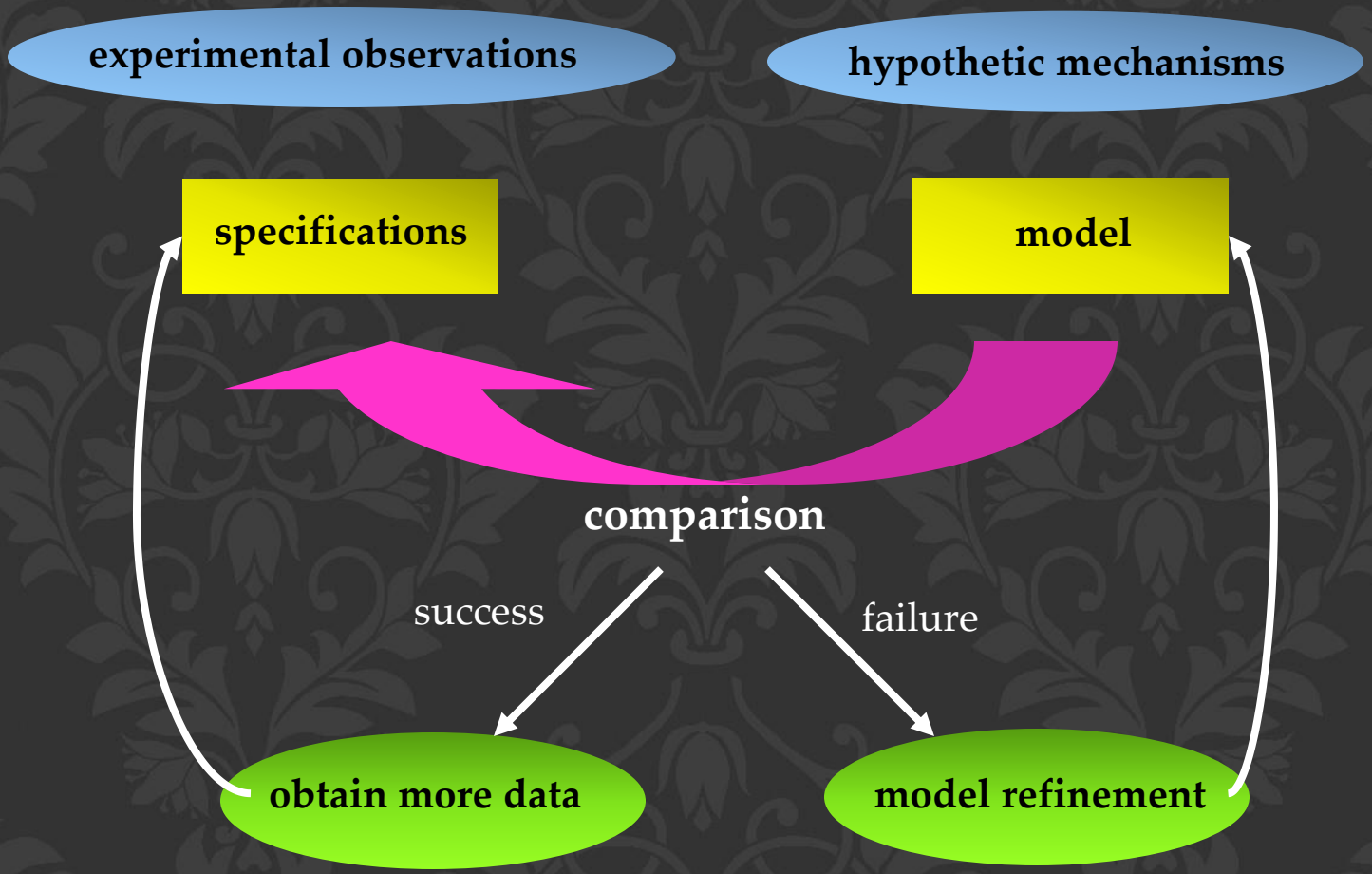
Provide a recipe for execution on a computer.

Fisher J. & Henzinger T.A. *Nature Biotechnology* (2007) **25**(11):1239-1249

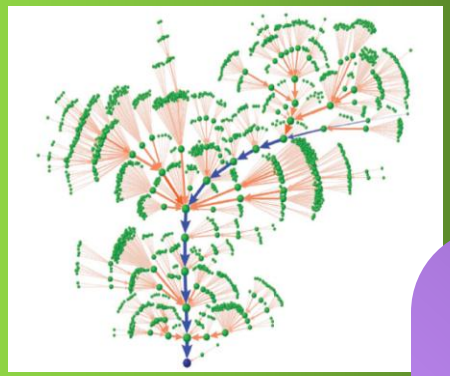
Scientific Method



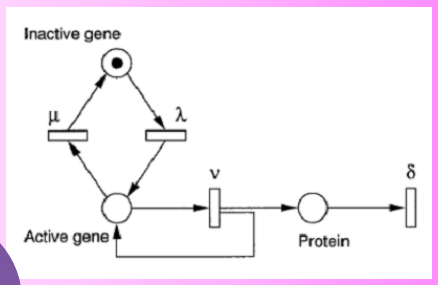
Bio-CEGAR


experimental observations
hypothetic mechanisms
specifications
model
comparison
success
failure
obtain more data
model refinement

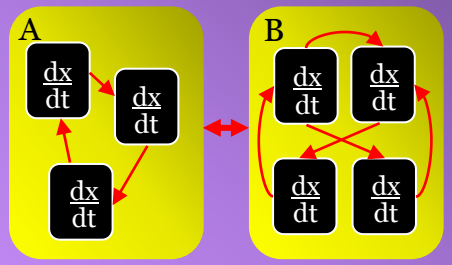
Models for Executable Biology



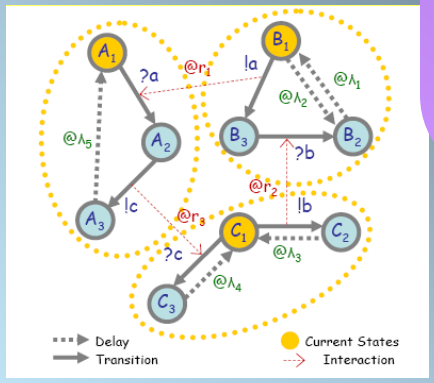
Qualitative networks



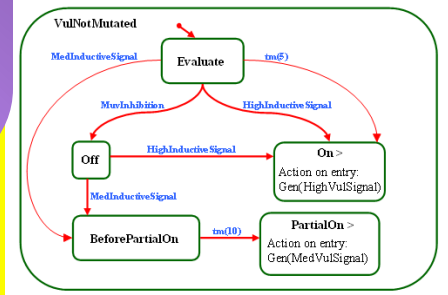
Petri nets



Hybrid models

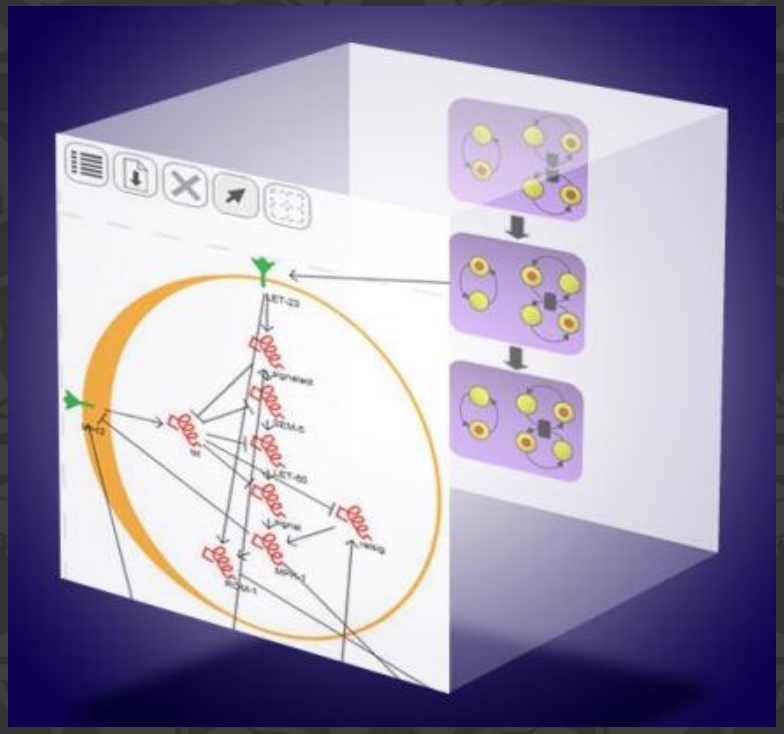


Pi calculus



State-machines

Modelling biological regulatory networks using Qualitative Networks



Qualitative Networks

- Extension of Boolean networks
- Larger range of possible values
- More flexible target functions
- Modelling of hierarchy
- Increased sophistication in analysis
- Bio Model Analyzer

Schaub *et al., BMC Systems Biology* (2007)

Schaub *et al., RECOMB Systems Biology LNBI* (2008)

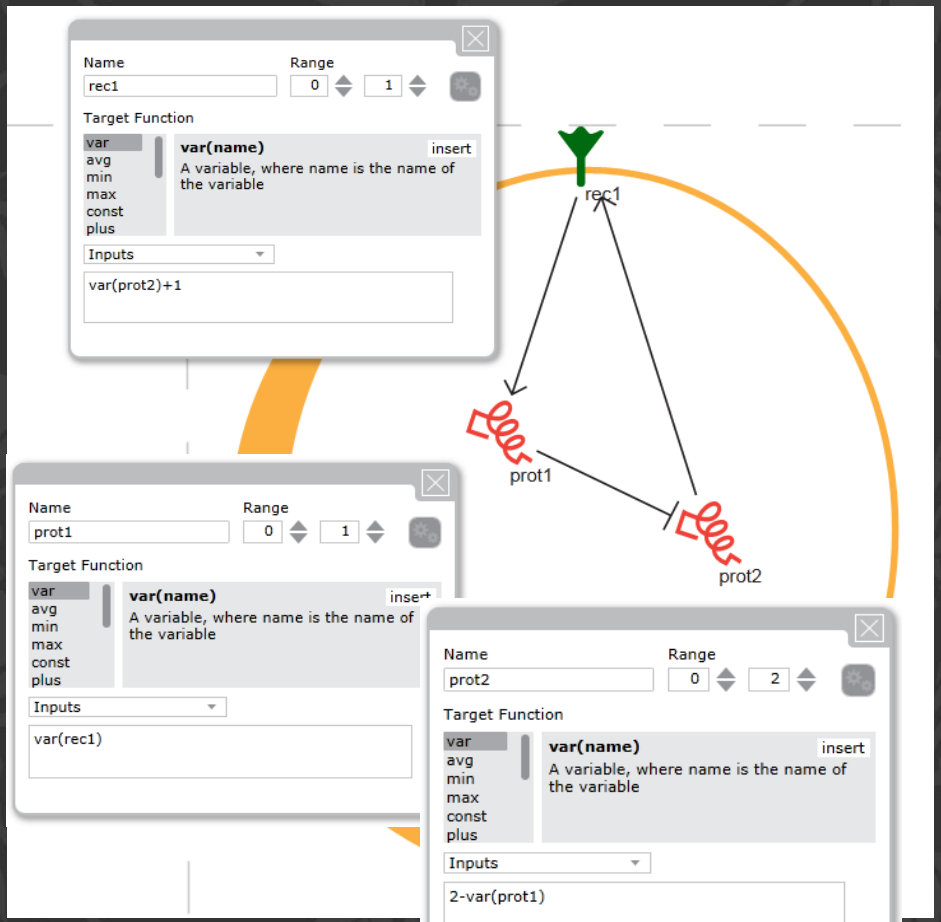
Cook *et al., VMCAI* (2011)

Benque *et al., CAV* (2012)

…more formally:

A *qualitative network* (QN) is $Q = (V, T, N)$, where $V = (v_1, v_2, \ldots, v_n)$ is a set of variables ranging over $\{0,1, \ldots, N\}$ and $T = (T_1, \ldots, T_n)$ are their respective target functions.

A state of the system is an assignment $s: V \rightarrow \{0,1, \ldots, N\}$. Let Σ denote the set of all possible states.



rec1 0 : prot1 0 : prot2 2

rec1 0 : prot1 0 : prot2 1

rec1 0 : prot1 0 : prot2 0

rec1 1 : prot1 0 : prot2 2

rec1 1 : prot1 0 : prot2 1

rec1 1 : prot1 1 : prot2 2

rec1 1 : prot1 1 : prot2 0

rec1 1 : prot1 1 : prot2 1

rec1 0 : prot1 1 : prot2 2

rec1 1 : prot1 0 : prot2 0

rec1 0 : prot1 1 : prot2 0

rec1 0 : prot1 1 : prot2 1

…more formally:

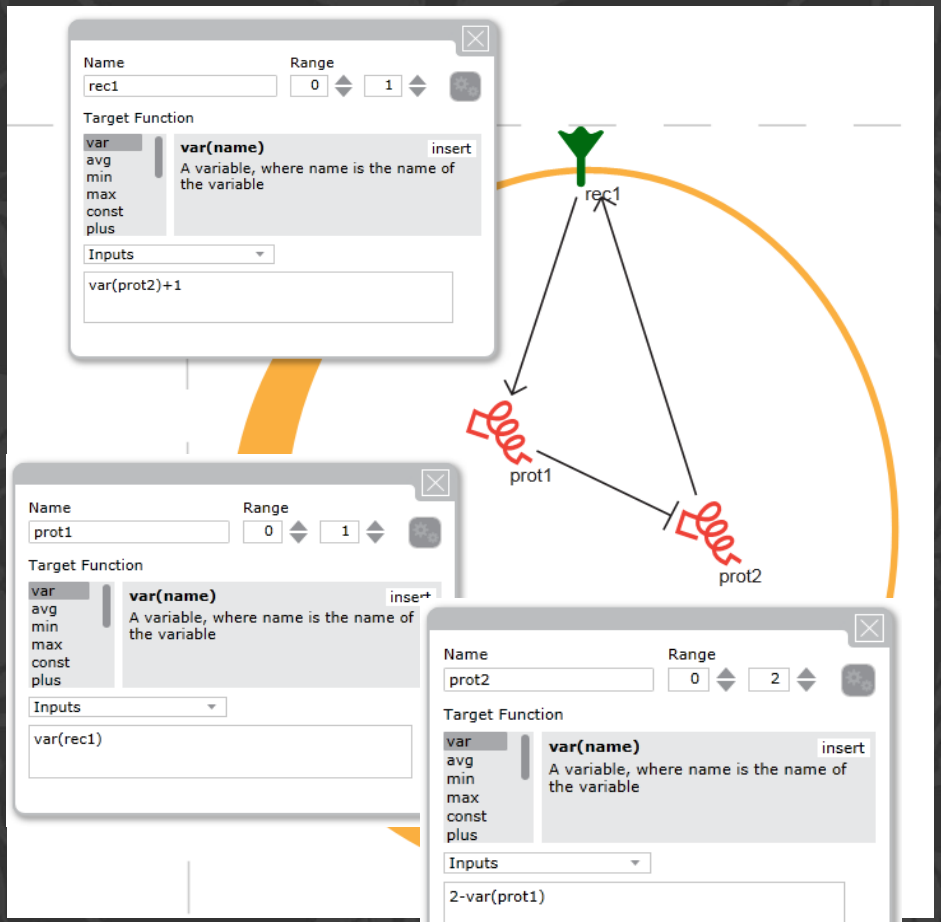
A ***qualitative network*** (QN) is $Q = (V, T, N)$, where $V = (v_1, v_2, \ldots, v_n)$ is a set of variables ranging over $\{0,1, \ldots, N\}$ and $T = (T_1, \ldots, T_n)$ are their respective target functions.

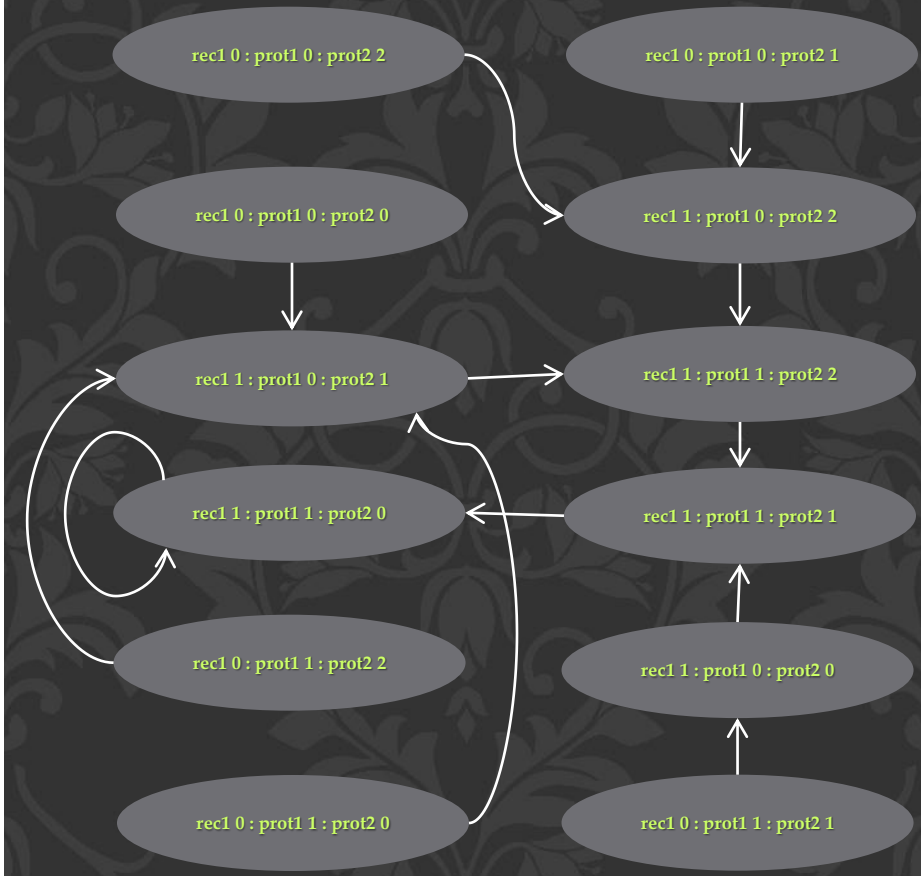
A state of the system is an assignment $s: V \rightarrow \{0,1, \ldots, N\}$. Let Σ denote the set of all possible states.

A ***target function*** $T_i \in T$ is $T_i: \Sigma \rightarrow \{0,1, \ldots, N\}$. Intuitively, in a given state s, variable v_i "would like" to get the value $T_i(s)$. However, values of variables change by at most 1. The *successor* of state s is s', where for every $v_i \in V$ we have:

$$s'_i(v_i) = \begin{cases} s(v_i) + 1 & If\ s(v_i) < T_i(s)\ and\ s(v_i) < N \\ s(v_i) - 1 & If\ (v_i) > T_i(s)\ and\ s(v_i) > 0 \\ s(v_i) & Otherwise \end{cases}$$

Scalable analysis is possible through combination of static analysis and verification techniques.


Name
rec1
Range
0
1
Target Function
var
avg
min
max
const
plus
var(name)
insert
A variable, where name is the name of the variable
Inputs
var(prot2)+1
rec1
prot1
prot2
Name
prot1
Range
0
1
Target Function
var
avg
min
max
const
plus
var(name)
A variable, where name is the name of the variable
Inputs
var(rec1)
Name
prot2
Range
0
2
Target Function
var
avg
min
max
const
plus
var(name)
insert
A variable, where name is the name of the variable
Inputs
2-var(prot1)

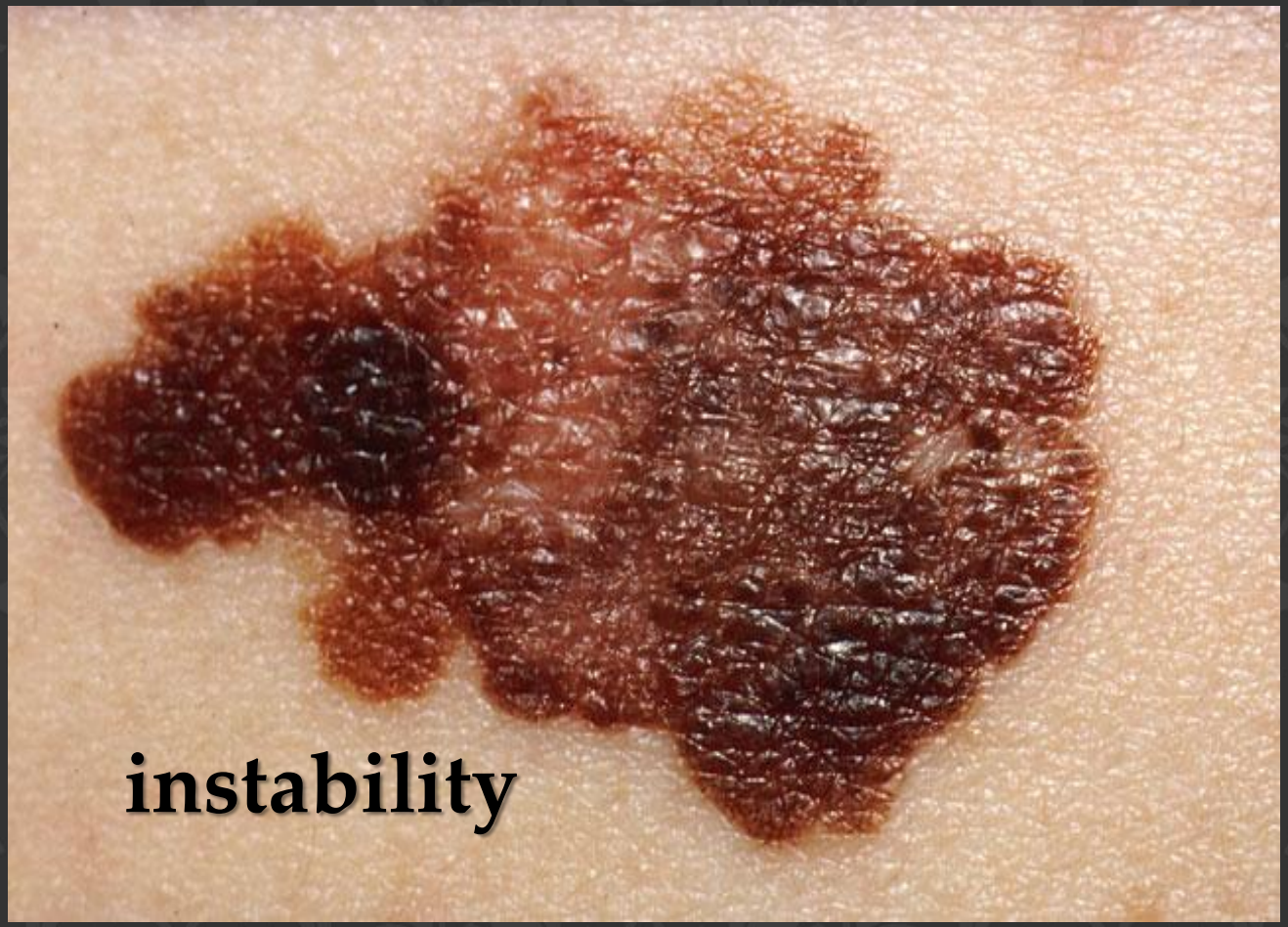

rec1 0 : prot1 0 : prot2 2
rec1 0 : prot1 0 : prot2 1
rec1 0 : prot1 0 : prot2 0
rec1 1 : prot1 0 : prot2 2
rec1 1 : prot1 0 : prot2 1
rec1 1 : prot1 1 : prot2 2
rec1 1 : prot1 1 : prot2 0
rec1 1 : prot1 1 : prot2 1
rec1 0 : prot1 1 : prot2 2
rec1 1 : prot1 0 : prot2 0
rec1 0 : prot1 1 : prot2 0
rec1 0 : prot1 1 : prot2 1

Executable modelling of cancer signalling in mammalian skin

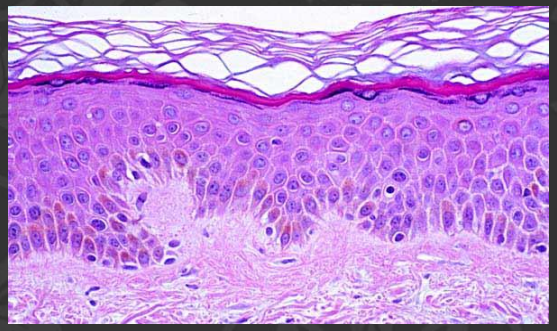
Freddy Radtke
EPFL

Marc Schaub
Stanford

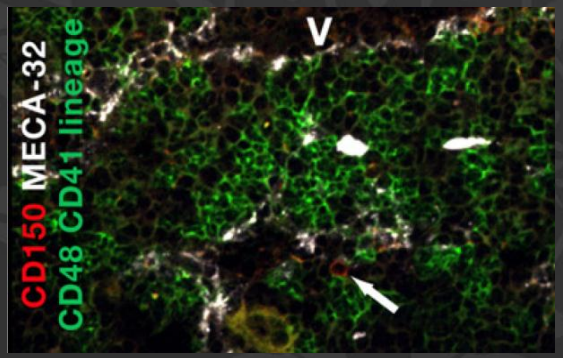
Mammalian skin (epidermis)



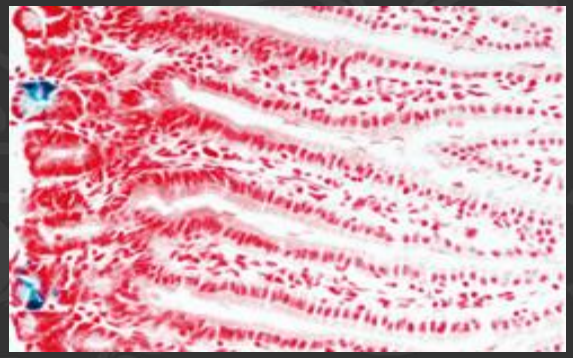
Tissue homeostasis is *critical*



Cells lost = new cells made

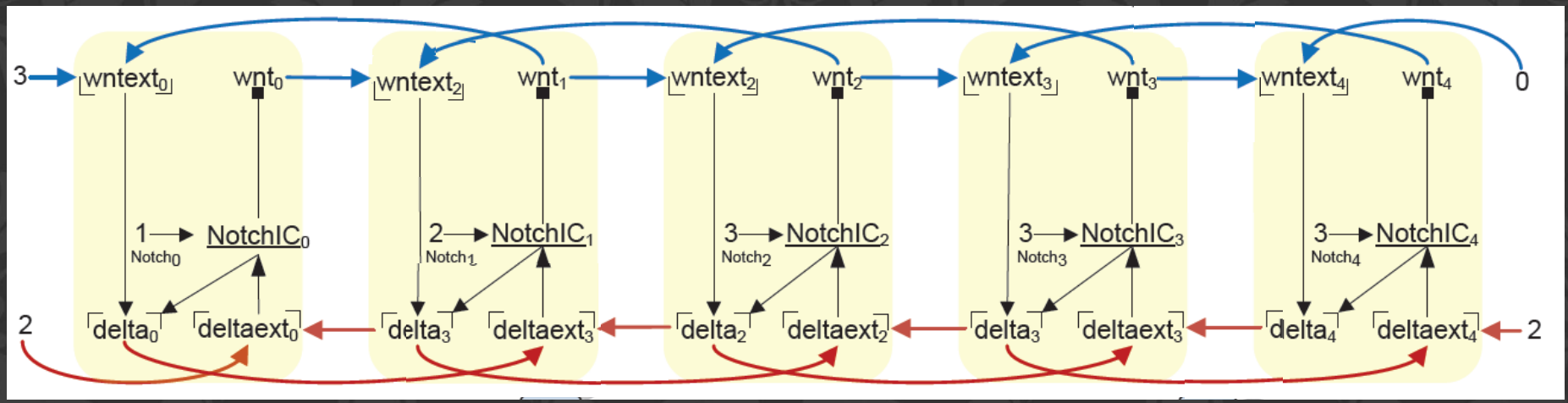


Cells lost > new cells made FAILURE



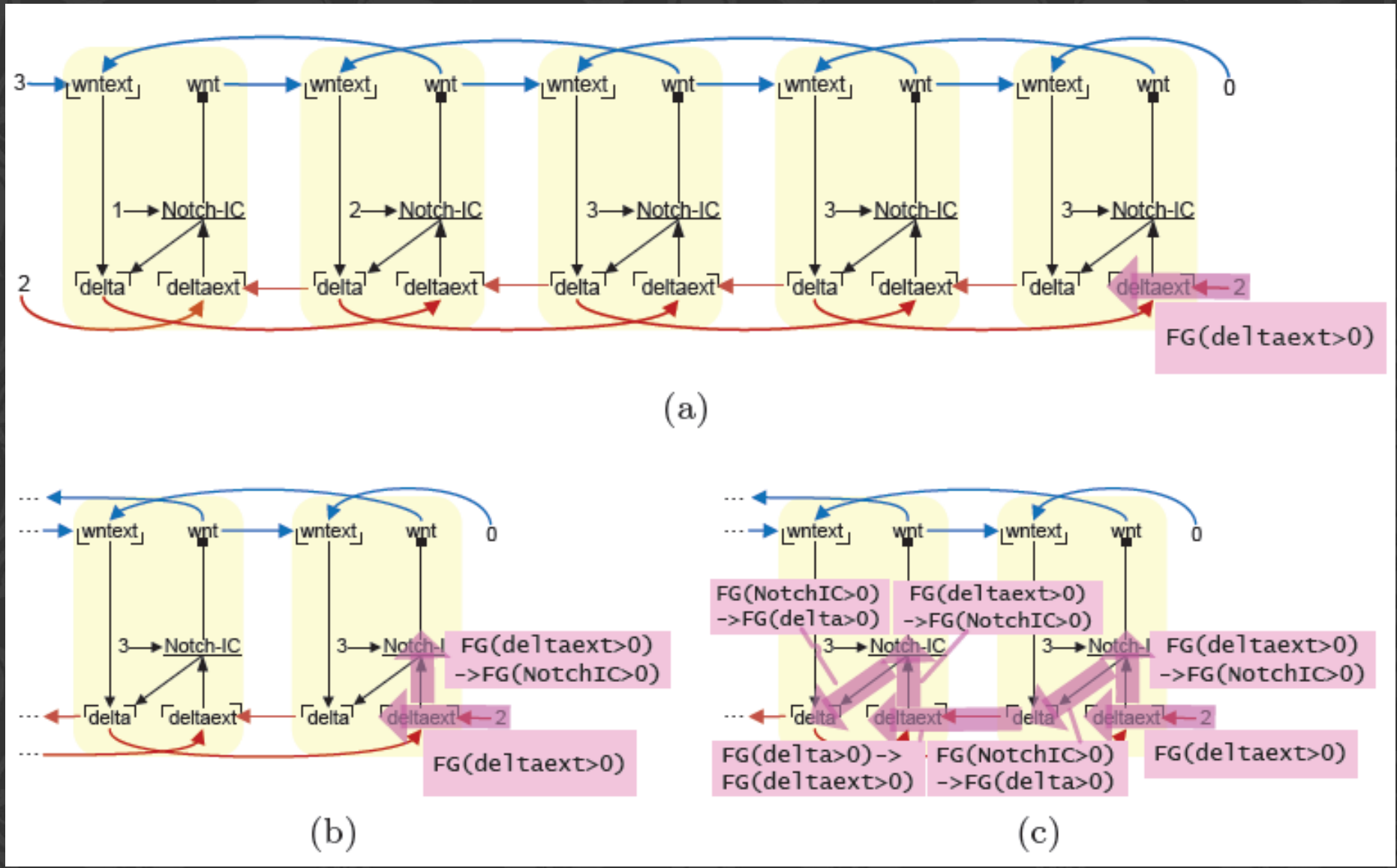
New cells made > cells lost CANCER

Mammalian skin model

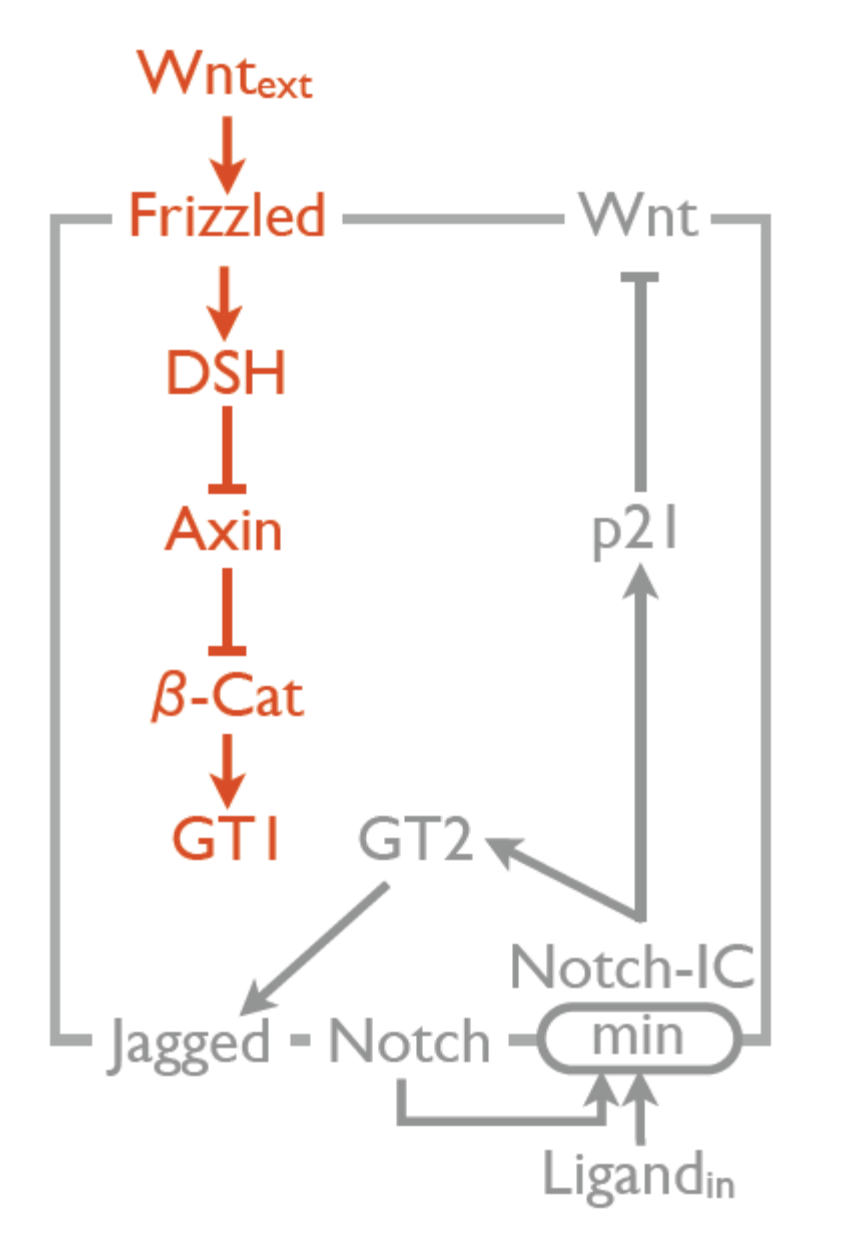


Does there exist a unique fix point that is eventually reached?

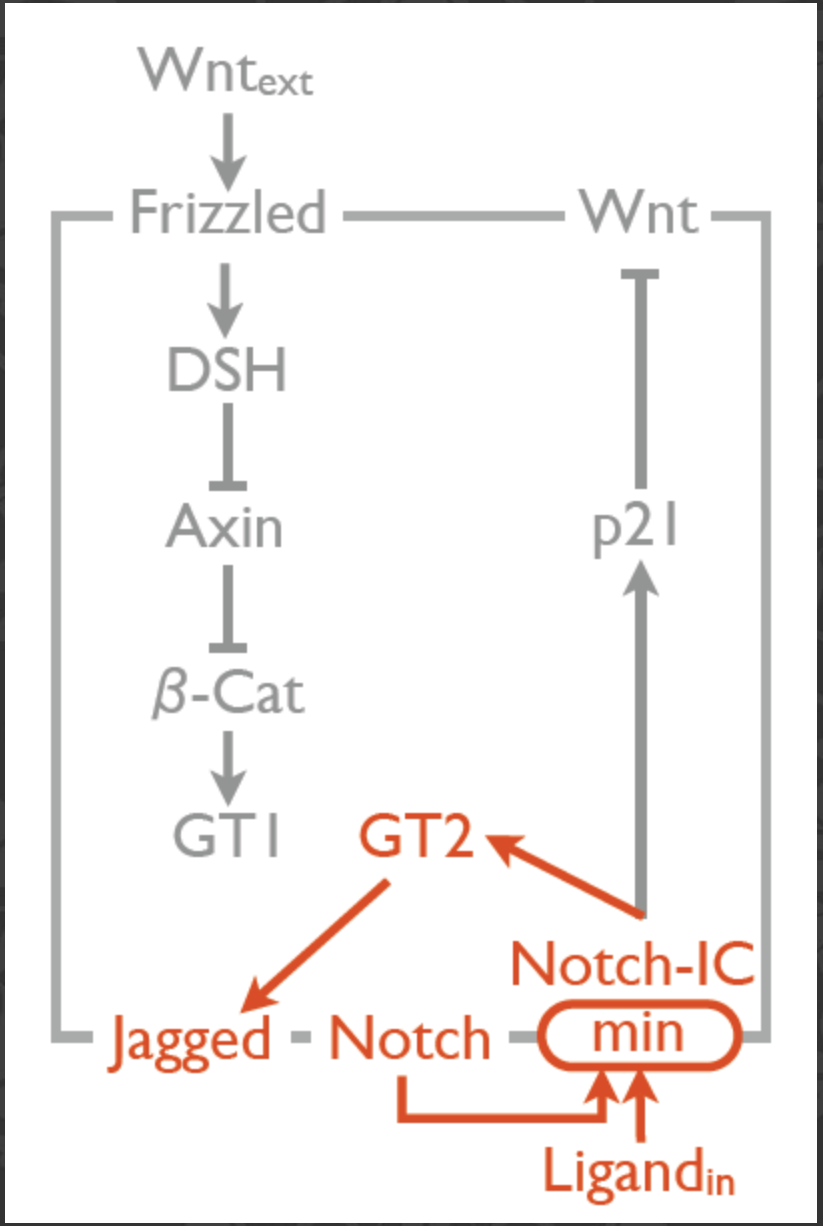
Geographic Proof



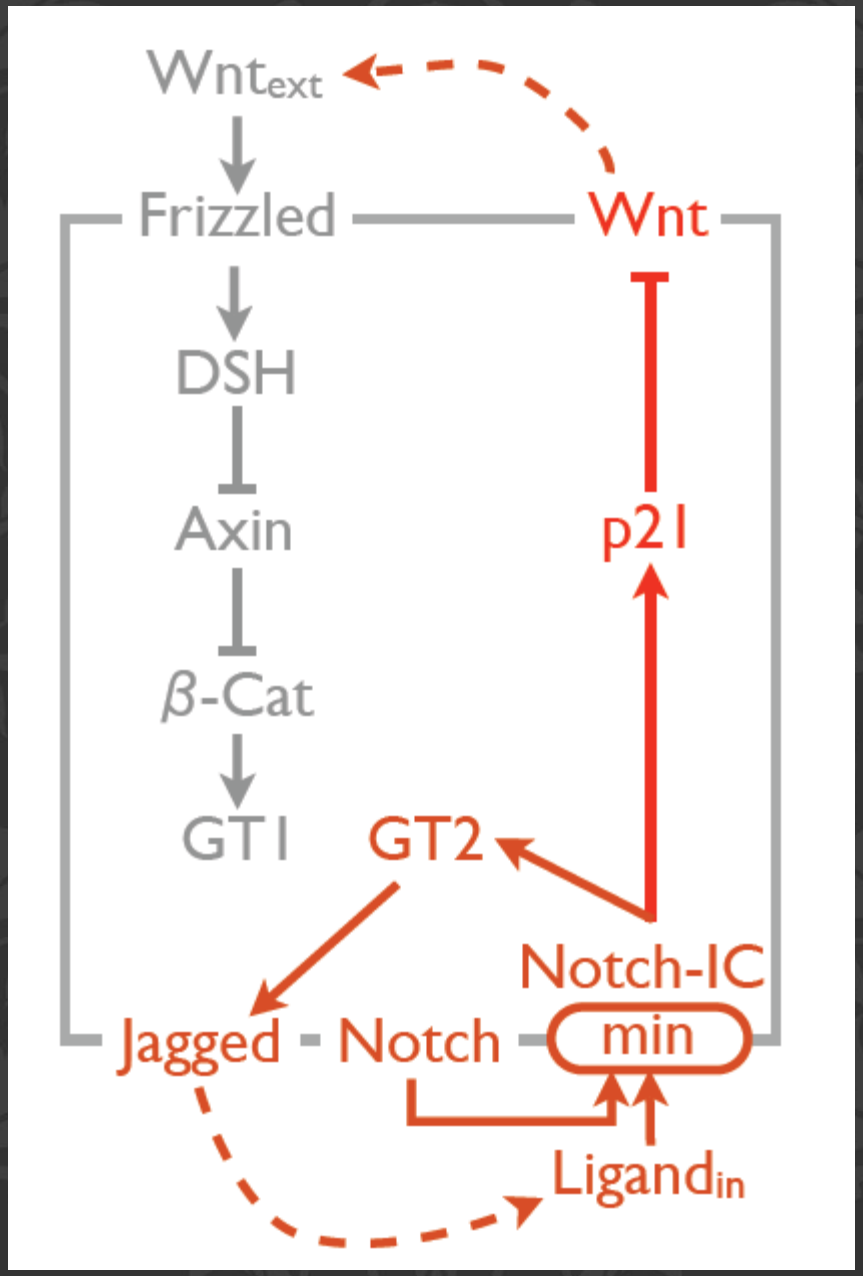
Wnt pathway


Wnt$_{ext}$
Frizzled
DSH
Axin
β-Cat
GT1
GT2
Wnt
p21
Notch-IC
min
Jagged
Notch
Ligand$_{in}$

Notch pathway



Crosstalk between Notch & Wnt



Requirements

Target genes of Wnt signaling (GT1) maintain the cell in a proliferating state.

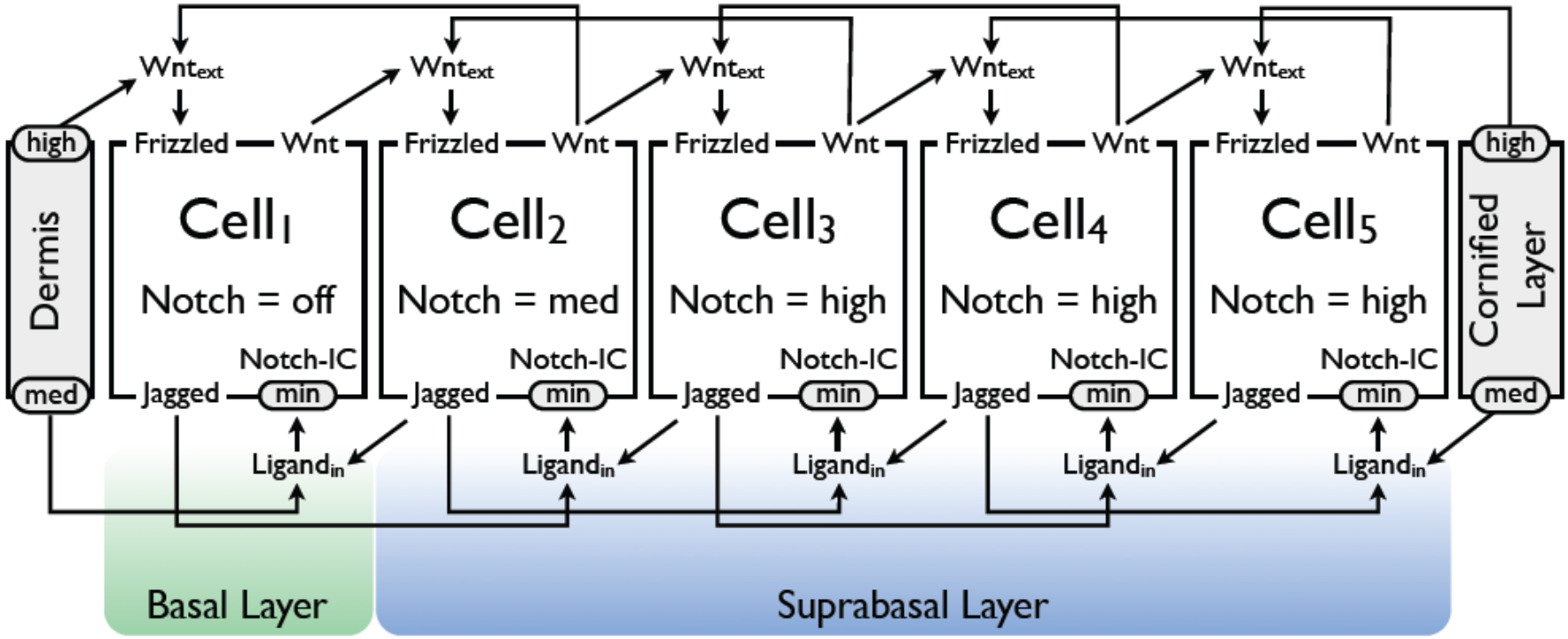
Target genes of Notch signaling (GT2) initiate terminal differentiation.

High-level requirements:

GT1 > GT2 → proliferation

GT1 < GT2 → differentiation

Model & Requirements



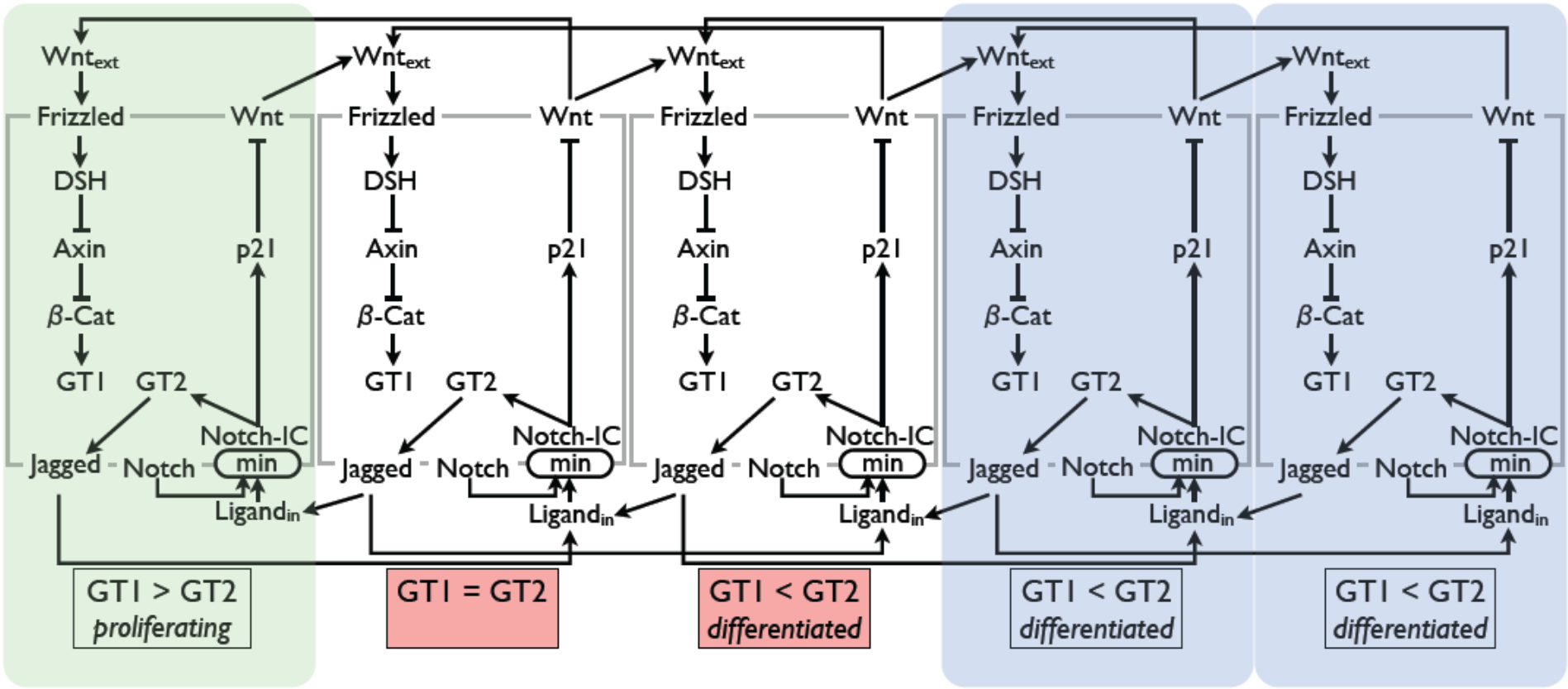
Requirements

GT1 > GT2	GT1 = GT2	GT1 < GT2	GT1 < GT2	GT1 < GT2
proliferating		*differentiated*	*differentiated*	*differentiated*

Schaub *et al., BMC Systems Biology* (2007) **1**:4; *RECOMB Systems Biology LNBI (2008)*

Gaining new biological insights…

Analysis

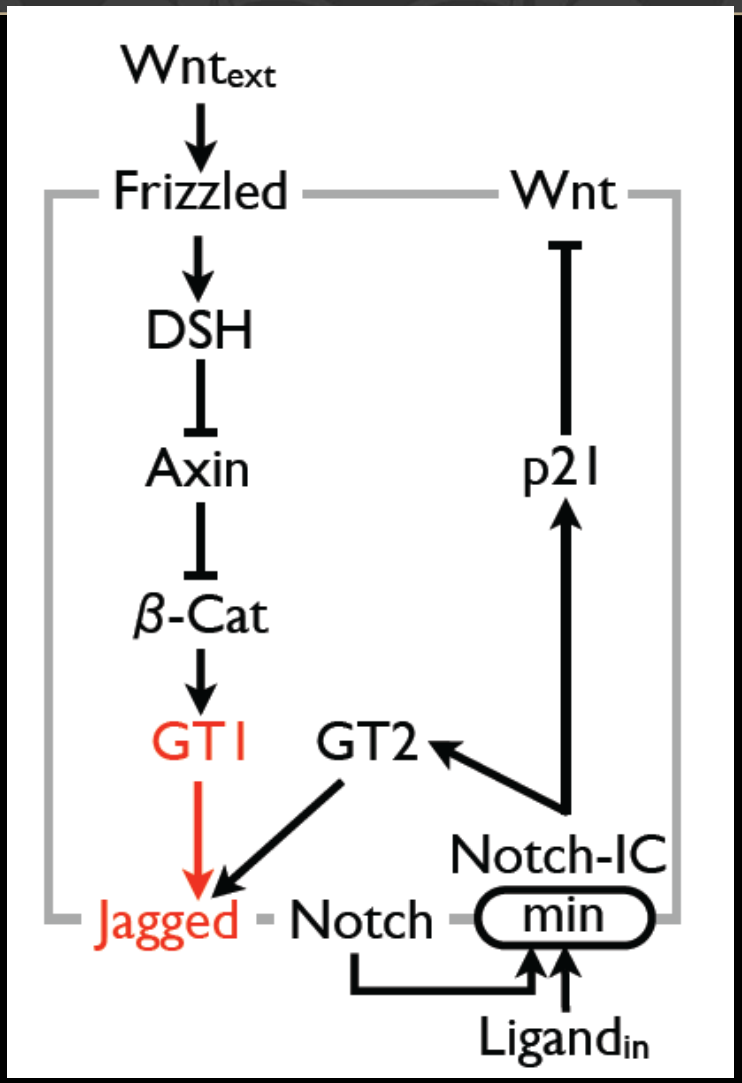


- 6561 infinitely visited states.
- Requirements on cells 1,4,5 are satisfied.
- Requirements on cells 2,3 are not satisfied.

Schaub *et al., BMC Systems Biology* (2007) **1**:4; *RECOMB Systems Biology LNBI (2008)*

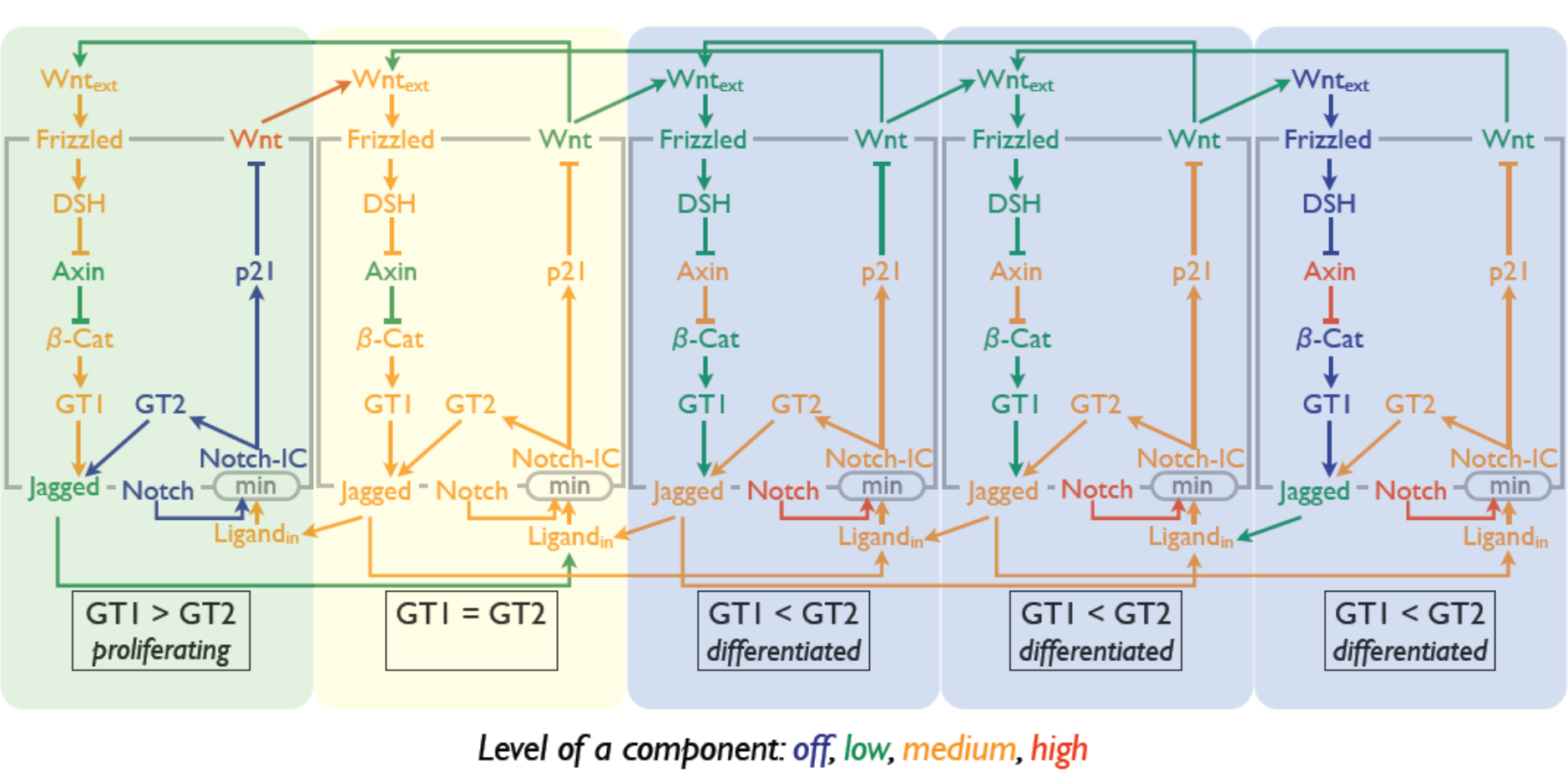
New Hypothesis:

Jagged is a downstream target of Wnt signaling



Schaub *et al., BMC Systems Biology* (2007) **1**:4; *RECOMB Systems Biology LNBI (2008)*

Analysis

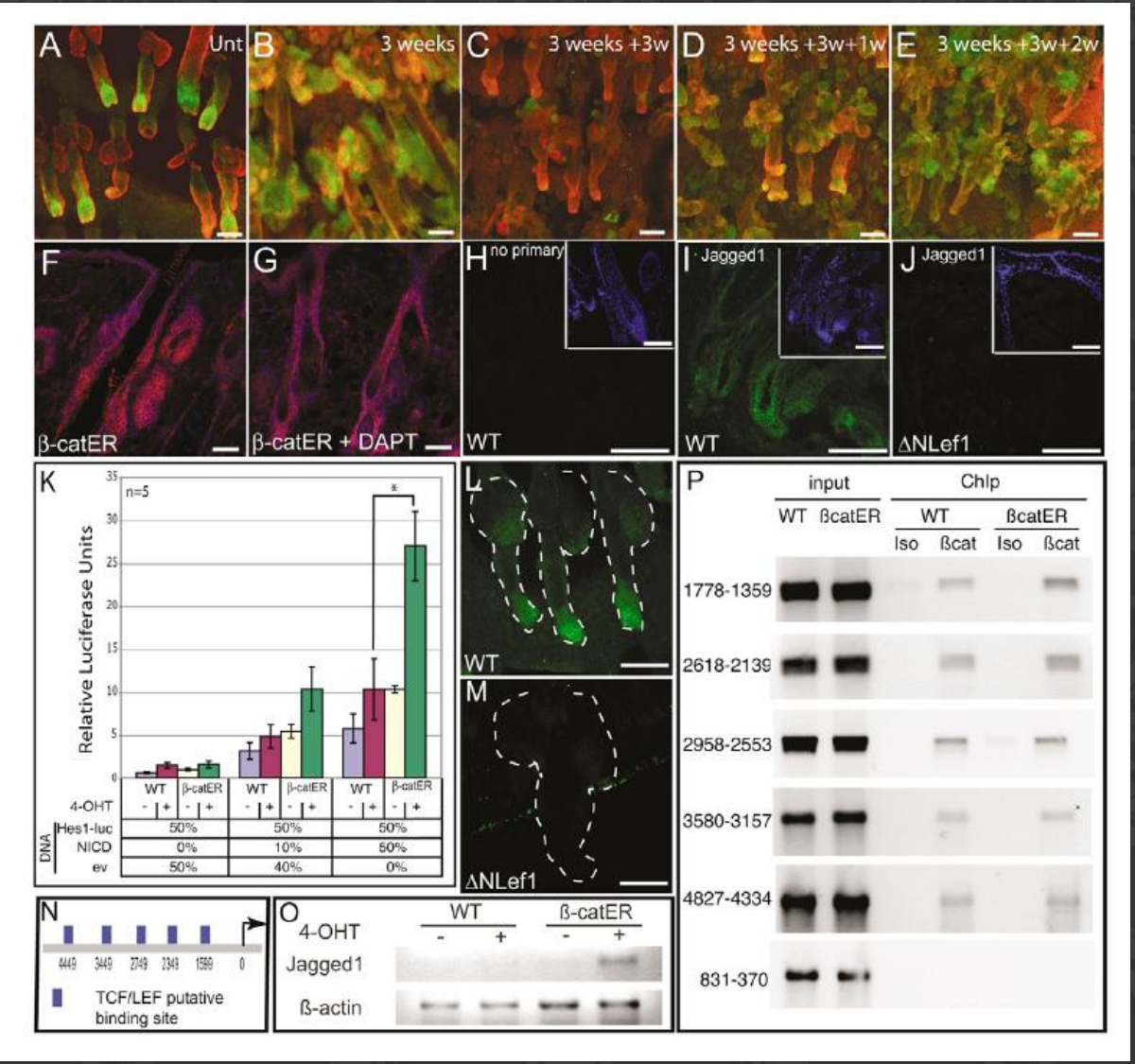


- One infinitely visited state.
- Satisfies all requirements.

Schaub *et al.*, *BMC Systems Biology* (2007) **1**:4; *RECOMB Systems Biology LNBI (2008)*

Experimental validation

Jag1 is a direct target gene of β-catenin



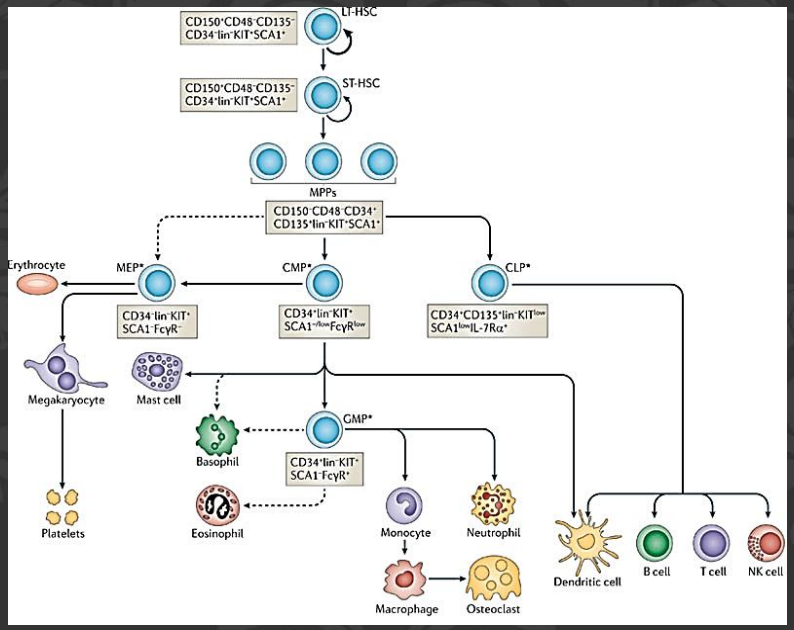
Estrach *et al.*, *Development* (2006)

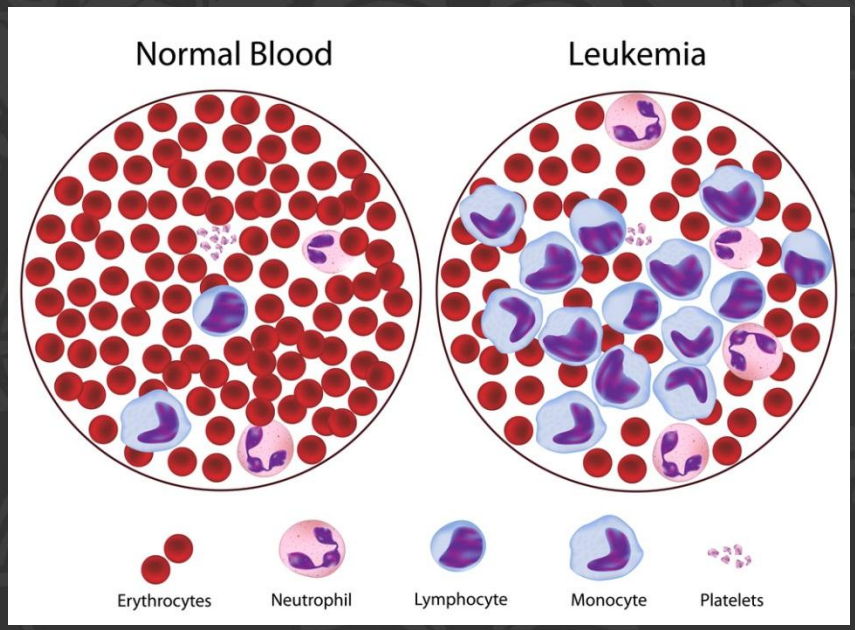
Executable modelling of blood cell development from pluripotent embryonic stem cells

Bertie Gottgens
Cambridge Institute for Medical Research

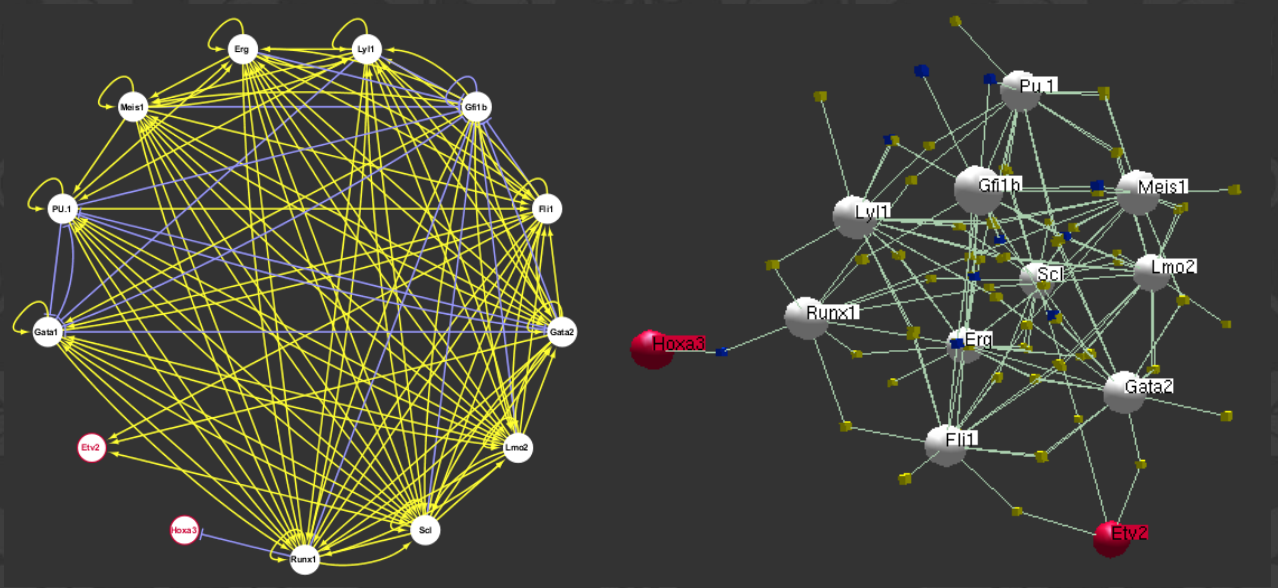
Lucinda Moore
University of Cambridge

How does normal blood stem cell development turn into leukaemia?



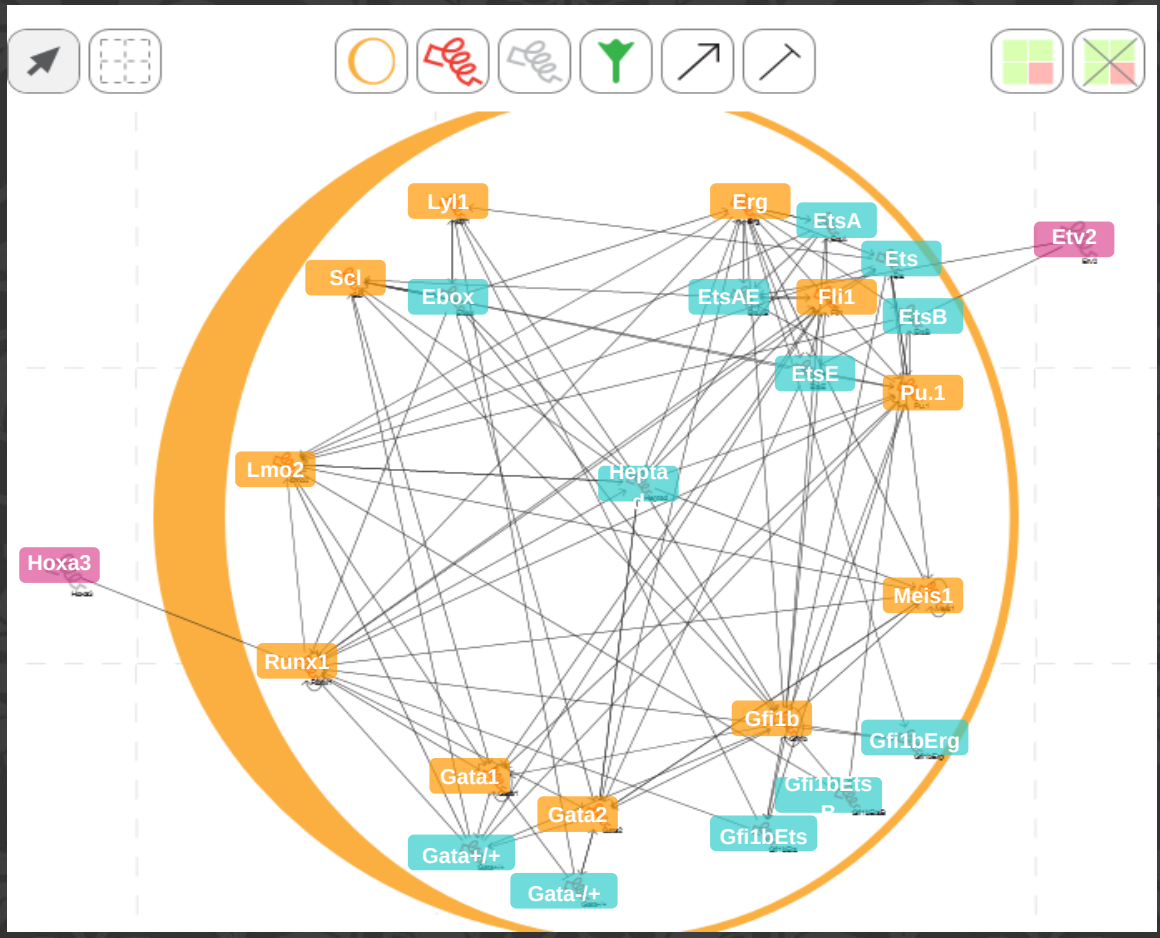


The grand challenge of analysing highly-connected gene regulatory networks

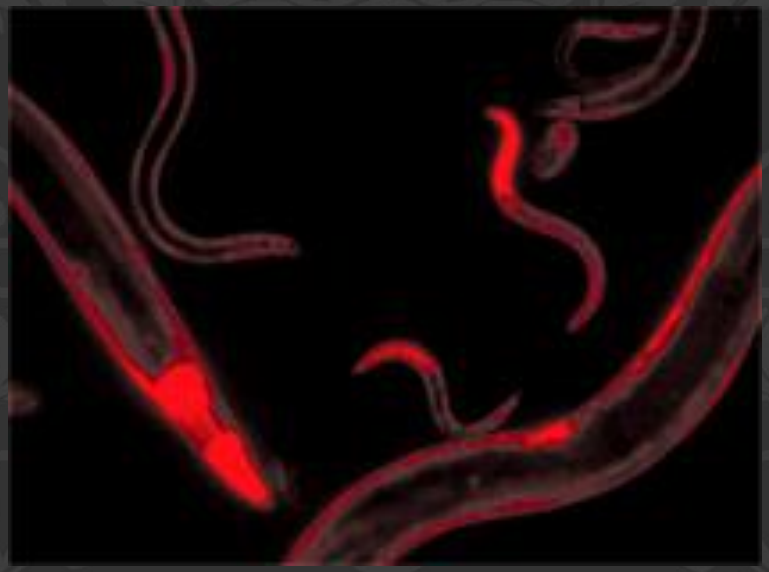


Genes regulating haematopoiesis

Mechanistic insights into leukaemia development



Modelling Cancer Signalling using State-machines



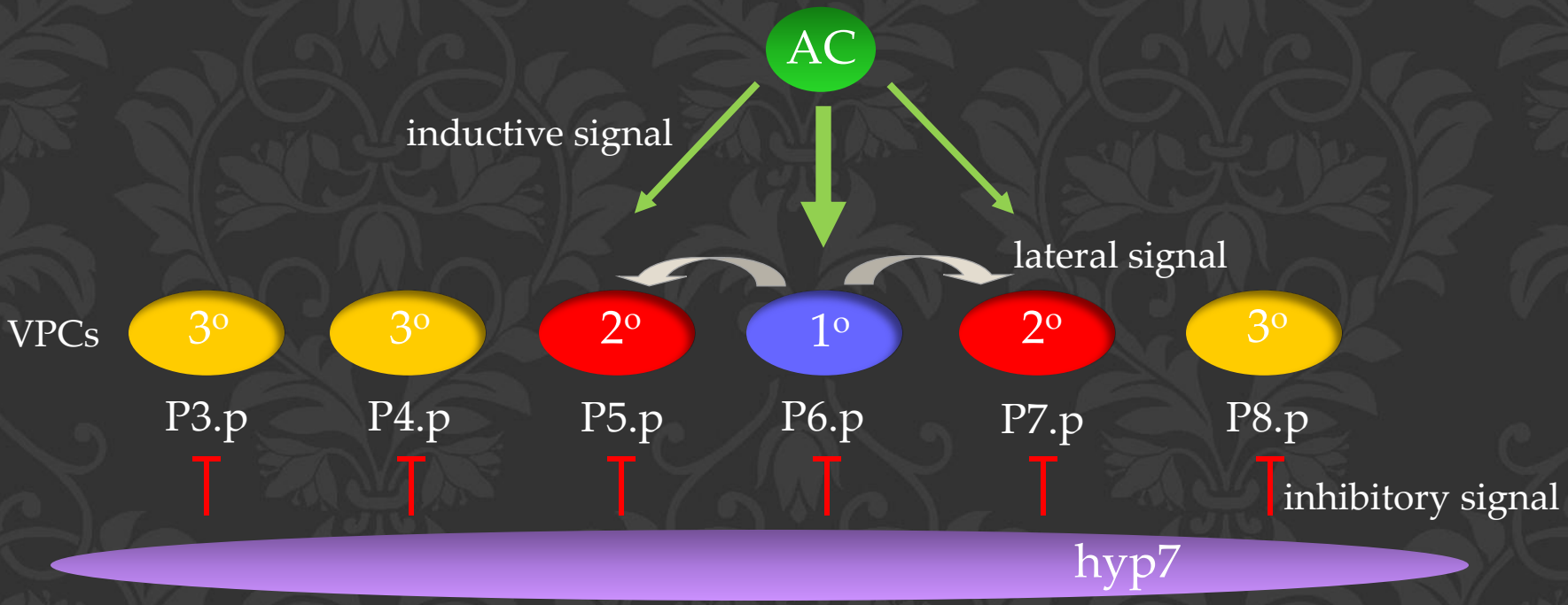
PNAS (2005) **102** (6): 1951-1956

PLoS Comp. Biol. (2007) **3**(5):e92

Mol Sys Biol (2012) **8**:618

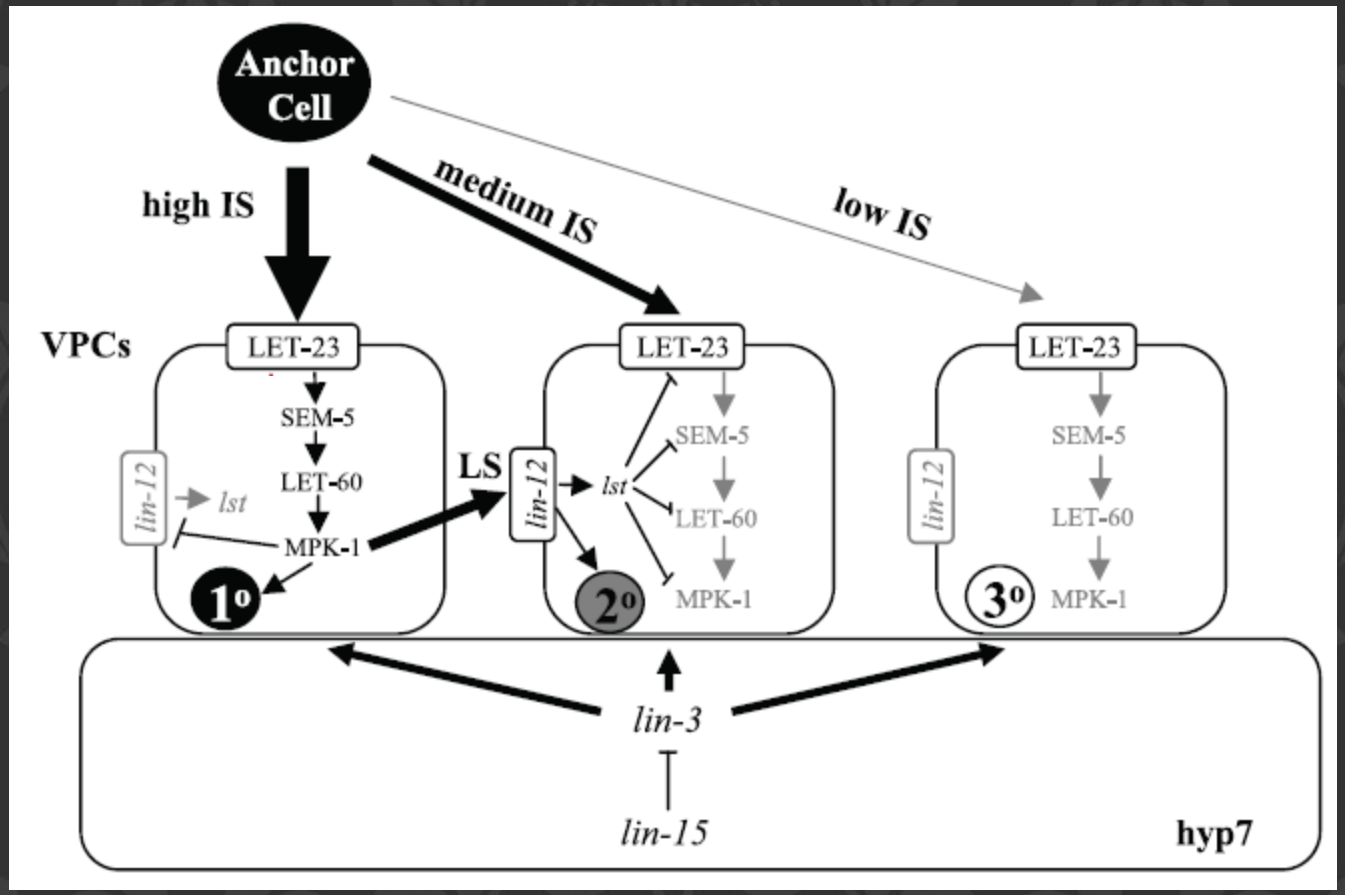
Caenorhabditis elegans (C. elegans)

- 1mm long worm
- ~ 1000 cells
- transparent
- easy to handle in the lab
- model for human biology
- very well studied


AC
inductive signal
lateral signal
VPCs
3°
3°
2°
1°
2°
3°
P3.p
P4.p
P5.p
P6.p
P7.p
P8.p
inhibitory signal
hyp7

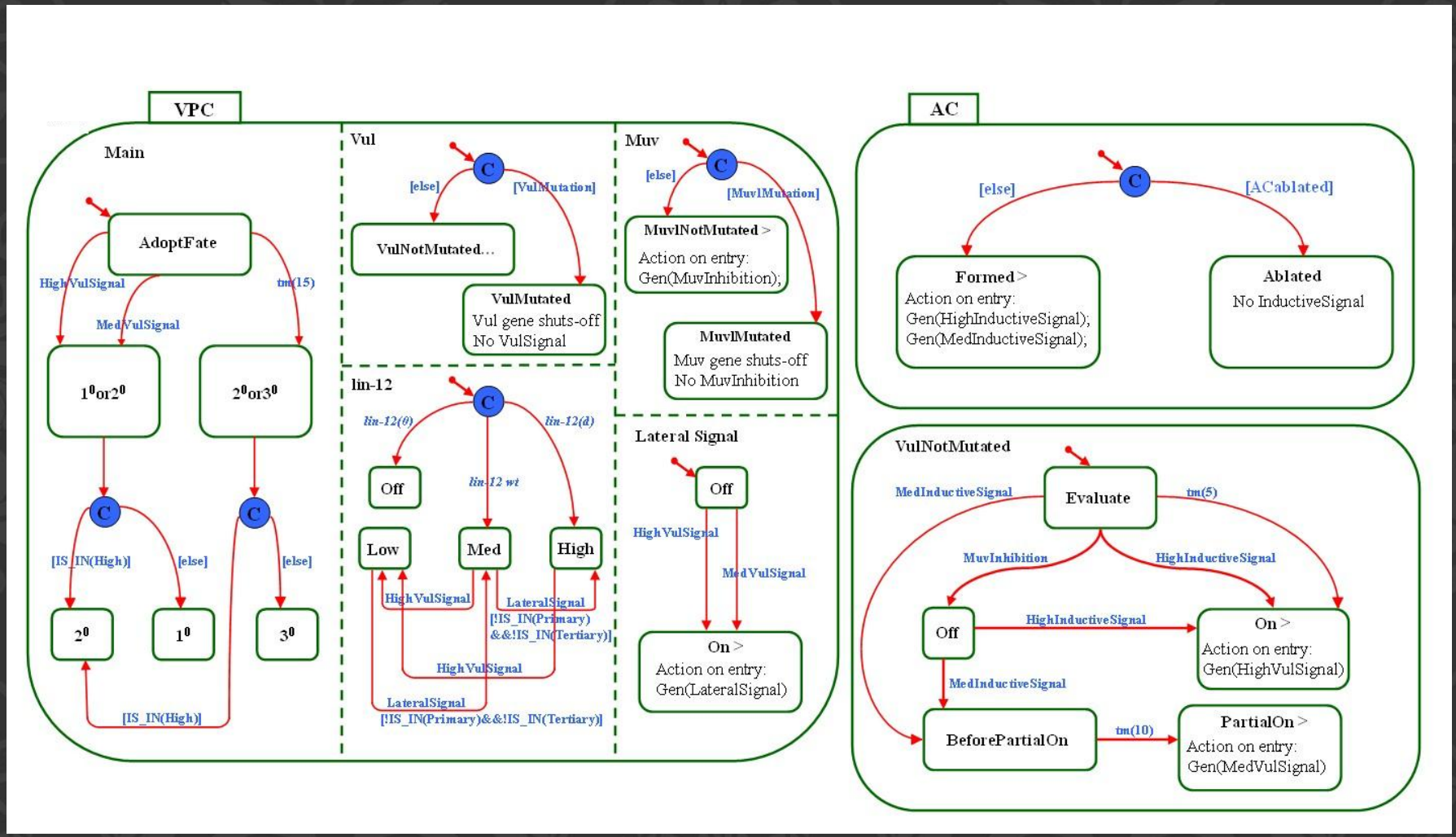
Conceptual understanding

Sternberg & Horwitz, '89; Berset et al., '01; Shaye & Greenwald, '02; Yoo et al., '04, Cui et al., '06



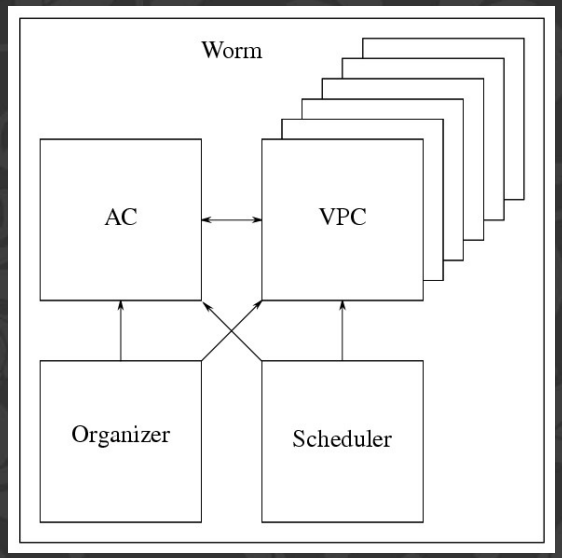
PLoS Comp. Biol. (2007) **3**(5):e92

Statecharts VPC Model

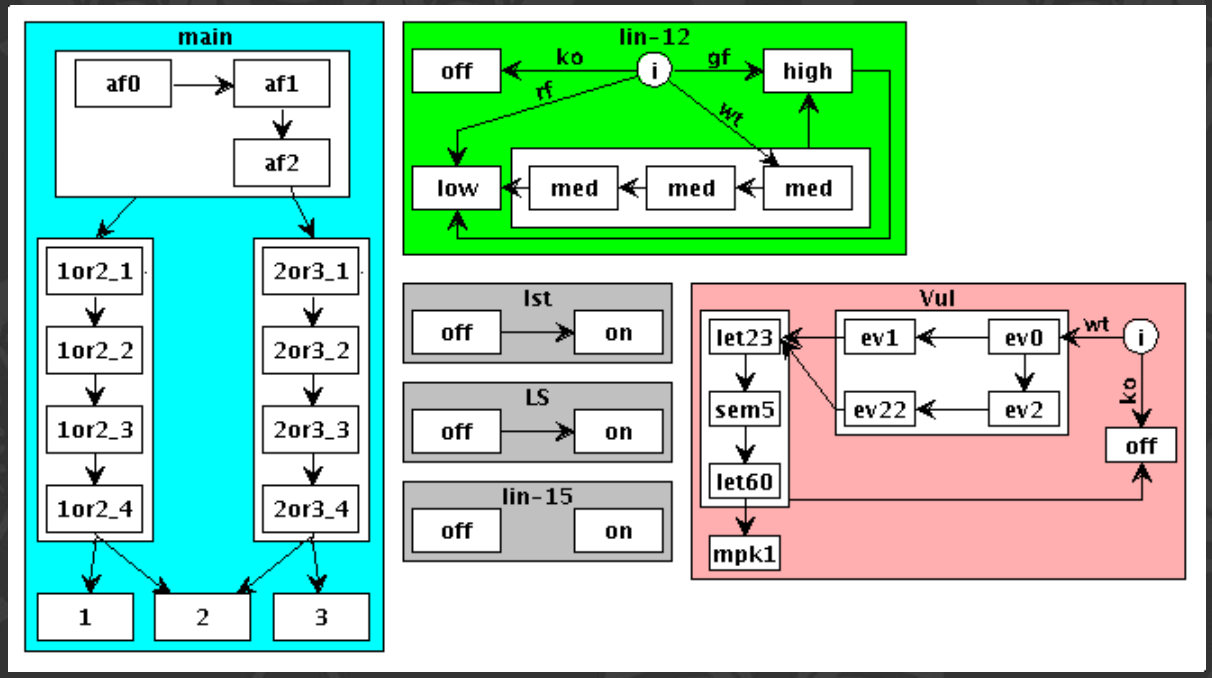


Fisher et al., *PNAS* (2005) **102** (6): 1951-1956

Interacting state-machine model of the worm vulva



Modules comprising the Worm Vulva model



Fisher *et al., PLoS Comp. Biol.* (2007) **3**(5):e92

Experimental observations

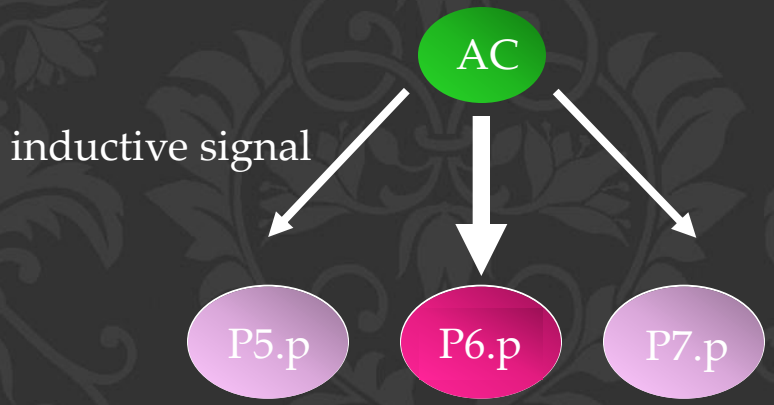
Table 4. Summary of VPC Fates

		lin-2(d)						Wild Type						*lin-12(0)*					
		P3.p	P4.p	P5.p	P6.p	P7.p	P8.p	P3.p	P4.p	P5.p	P6.p	P7.p	P8.p	P3.p	P4.p	P5.p	P6.p	P7.p	P8.p
Muv	ac$^+$	2	1/2	2	ac 1 —	2	1/2	1/2	1/2	2	ac 1 —	2	1/2	1	1	1	acac 1 —	1	1
	ac$^-$	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1	1	1	1	?	1
+	ac$^+$	2	2	2	ac 1 —	2	2	3	3	2	ac 1 —	2	3	3	3	1	acac 1 —	1	3
	ac$^-$	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3
Vul	ac$^+$	2	2	2	ac 2 —	2	2	3	3	3	ac 3 —	3	3	3	3	3	acac 3	3	3
	ac$^-$	2	2	2	2	2	2	3	3	3	3	3	3	ND					

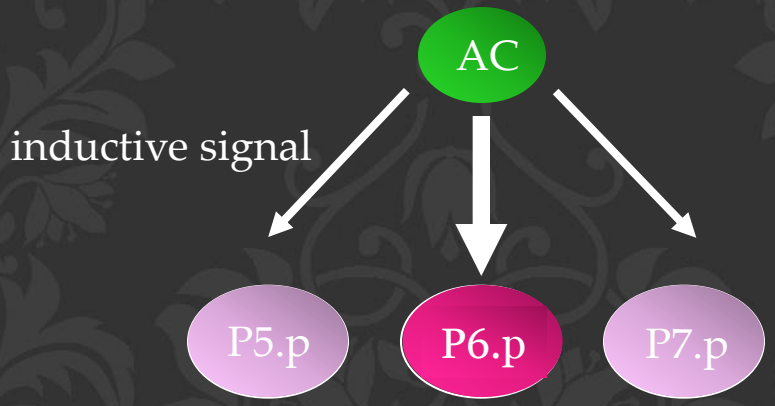
In the presence of AC when *Muv* & *lin-12* are mutated, P7.p becomes secondary

new biological insights…

Known: The inductive signal is spatially graded



New insight: A temporally-graded response to the inductive signal

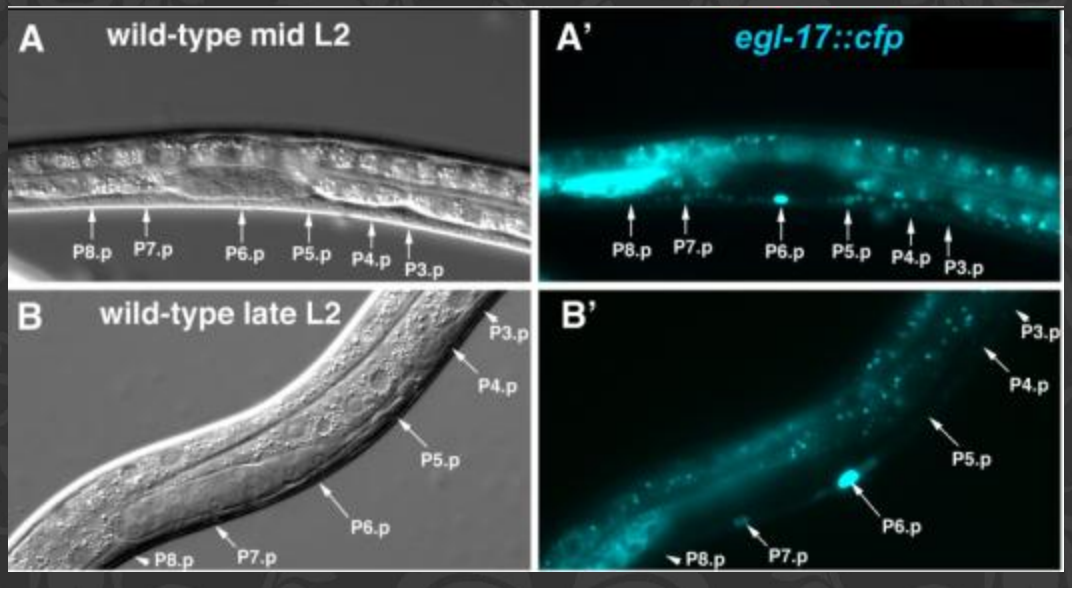


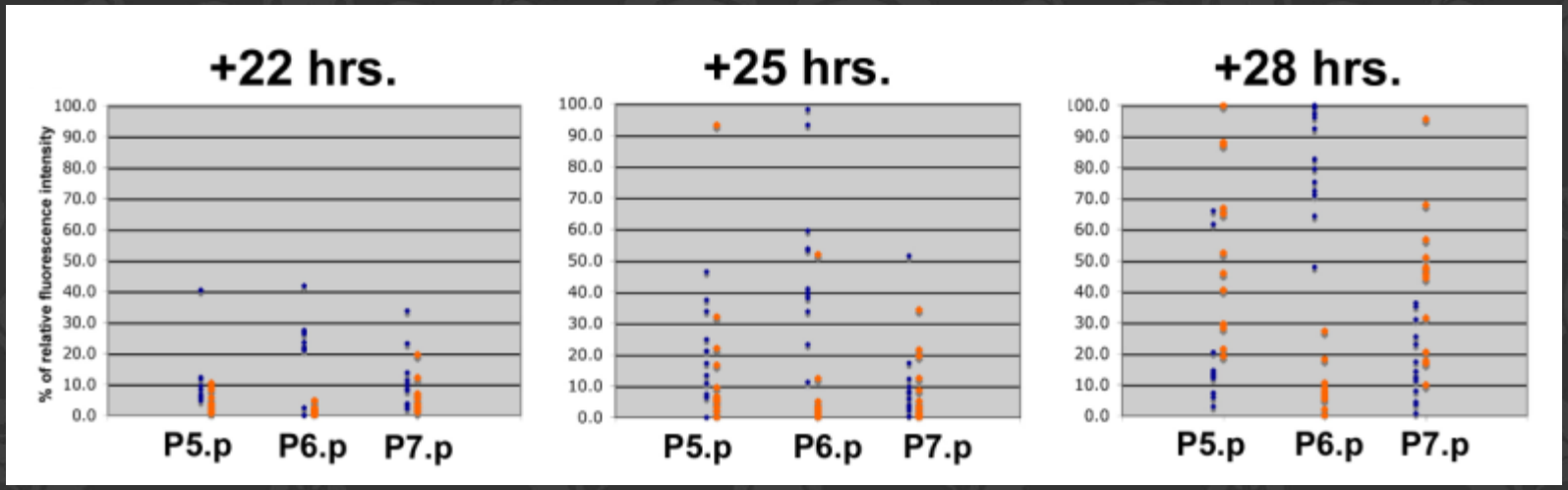
Fisher *et al., PNAS* (2005) **102** (6): 1951-1956

Experimental validation of the model's predictions

Temporal gradient activation of inductive signaling in wild-type animals

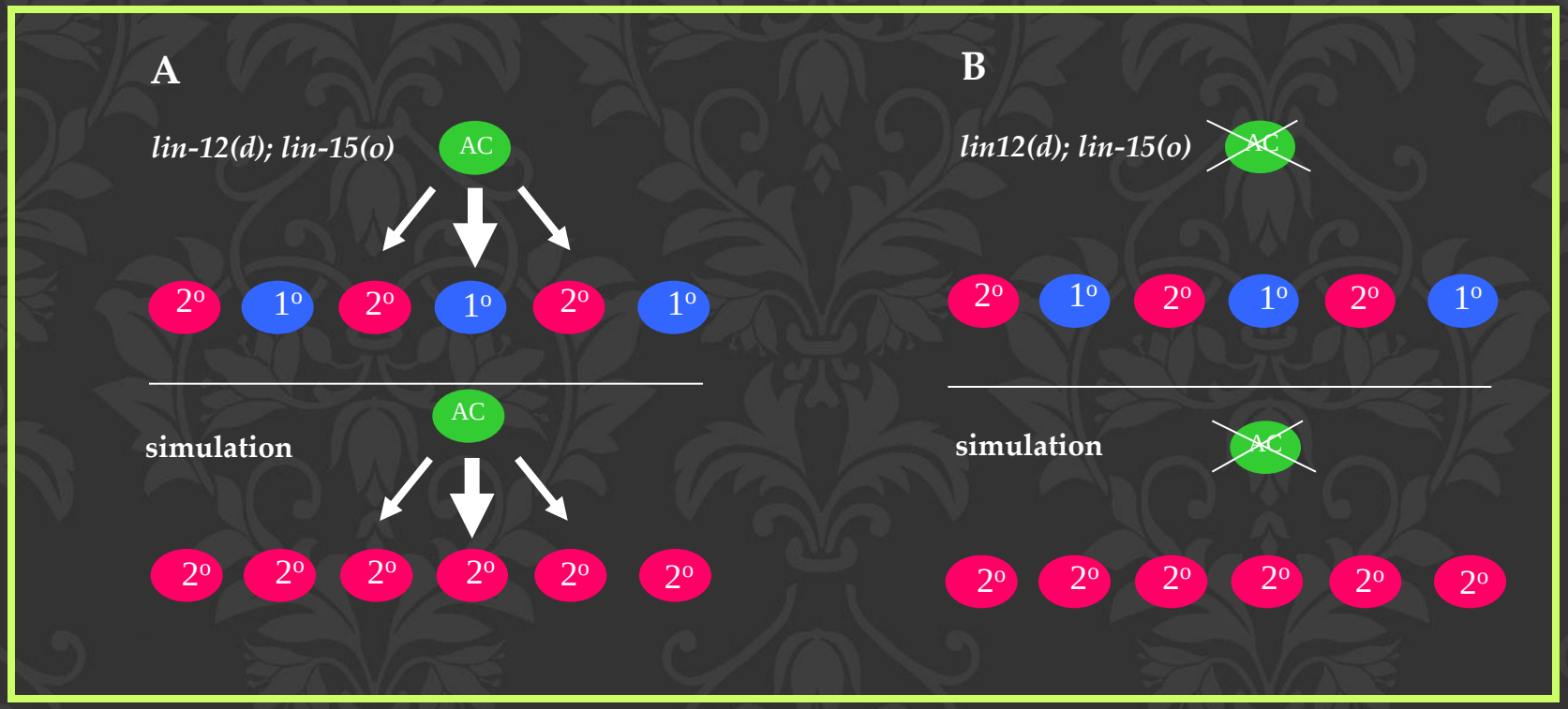
Together with
A. Hajnal





Fisher *et al., PLoS Comp. Biol.* (2007) **3**(5):e92

Analyzing the behavior of *lin-12(d);lin-15(o)* mutants

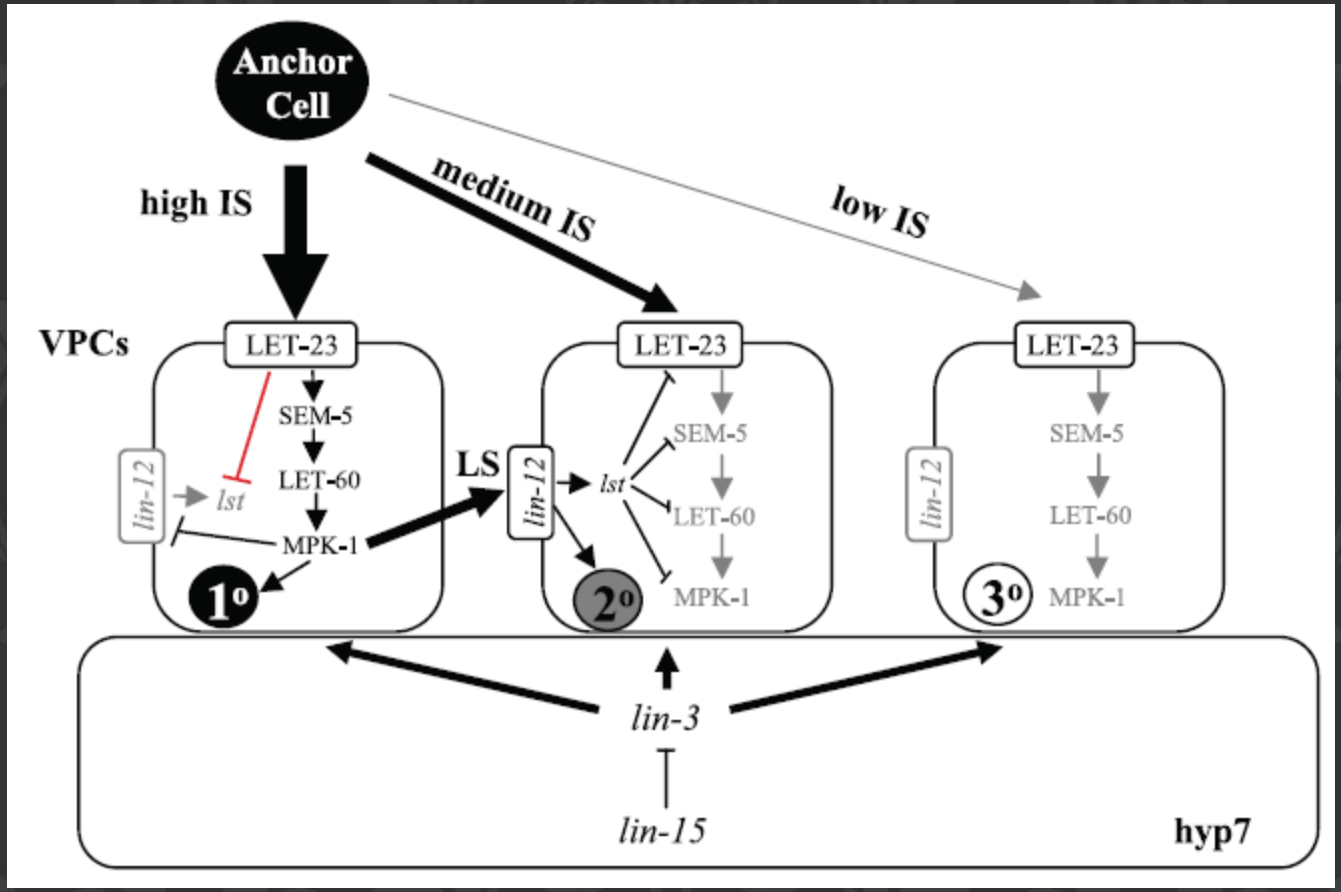


Fisher *et al., PLoS Comp. Biol.* (2007) 3(5):e92

Predicting a new negative feedback loop:

EGFR signaling negatively regulates *lst* gene activity

new insight!



Fisher *et al., PLoS Comp. Biol.* (2007) 3(5):e92

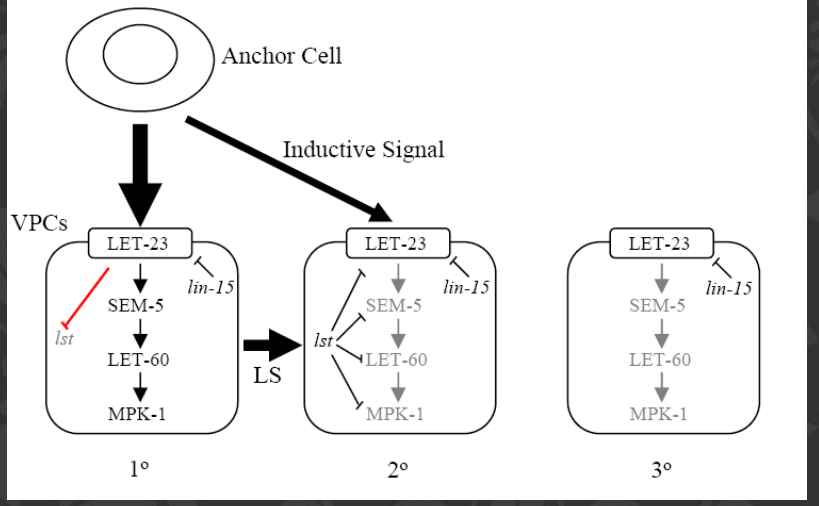
model-checking checks **ALL** possible runs of the model

observations

Table 4. Summary of VPC Fates

		lin-2(d)					
		P3.p	P4.p	P5.p	P6.p	P7.p	P8.p
Muv	ac⁺	2	1/2	2	ac 1	2	1/2
	ac⁻	1/2	1/2	1/2	— 1/2	1/2	1/2
+	ac⁺	2	2	2	ac 1	2	2
	ac⁻	2	2	2	— 2	2	2
Vul	ac⁺	2	2	2	ac 2	2	2
	ac⁻	2	2	2	— 2	2	2

model



MC

refinement

does the model satisfies the data?

yes

no

continue

get a counter example

model checking enables to **query** the system

e.g., do all possible executions reach a stable state, independent of the order of reactions between the VPCs ?

Summary of VPC fate patterns according to the computational model

	AC	lin12	lin15	Vul	lst	Predicate name	Fate pattern P3.p	P4.p	P5.p	P6.p	P7.p	P8.p	Reference & Remarks
1	formed	wt	wt	wt	wt	wild_type	3	3	2	1	2	3	Soulston & Horvitz '77
2	formed	wt	wt	wt	ko	lstko	3	3	1	1	1	3	Berset et al. '05, Yoo et al. '04 (by marker expression)
3	formed	wt	wt	ko	wt	Vulko	3	3	3	3	3	3	Sternberg & Horvitz '89
4	formed	wt	wt	ko	ko	Vulkolstko	3	3	3	3	3	3	n.d. (only partial Vul(rf) mutants tested)
5	formed	wt	ko	wt	wt	lin15ko	1\2	1\2	2	1	2	1\2	Sternberg & Horvitz '89
6	formed	wt	ko	wt	ko	lin15kolstko	1	1	1	1	1	1	Berset et al. '01(marker expression)
7	formed	wt	ko	ko	wt	lin15koVulko	3	3	3	3	3	3	Ferguson & Horvitz 87,Sternberg & Horvitz 89,Cui et al 06
8	formed	wt	ko	ko	ko	lin15koVulkolstko	3	3	3	3	3	3	n.d.
9	formed	ko	wt	wt	wt	lin12ko	3	3	1	1	1	3	Sternberg & Horvitz '89, Greenwald et al. '83
10	formed	ko	wt	wt	ko	lin12kolstko	3	3	1	1	1	3	Berset & Hajnal, unpublished results
11	formed	ko	wt	ko	wt	Vulkolin12ko	3	3	3	3	3	3	Sternberg & Horvitz '89 (rf Vul mutants)
12	formed	ko	wt	ko	ko	lin12koVulkolstko	3	3	3	3	3	3	n.d.
13	formed	ko	ko	wt	wt	lin15kolin12ko	1	1	1	1	1	1	Sternberg & Horvitz '89
14	formed	ko	ko	wt	ko	lin12kolin15kolstko	1	1	1	1	1	1	n.d.
15	formed	ko	ko	ko	wt	lin12kolin15koVulko	3	3	3	3	3	3	n.d.
16	formed	ko	ko	ko	ko	lin12kolin15koVulkolstko	3	3	3	3	3	3	n.d.
17	formed	gf	wt	wt	wt	lin12d	2	2	2	1	2	2	Sternberg & Horvitz '89 [lin-12(gf)/lin-12(lf)]
18	formed	gf	wt	wt	ko	lin12dlstko	2	2	1	1	1	2	n.d.
19	formed	gf	wt	ko	wt	Vulkolin12d	2	2	2	2	2	2	Sternberg & Horvitz '89 [(lin-12(gf)/lin-12(lf) with vul(rf)]
20	formed	gf	wt	ko	ko	lin12dVulkolstko	2	2	2	2	2	2	n.d.
21	formed	gf	ko	wt	wt	lin15kolin12d	1\2	1\2	2	1	2	1\2	Sternberg & Horvitz '89 [(lin-12(gf)/lin-12(lf)]
22	formed	gf	ko	wt	ko	lin12dlin15kolstko	1	1	1	1	1	1	n.d
23	formed	gf	ko	ko	wt	lin12dlin15koVulko	2	2	2	2	2	2	n.d
24	formed	gf	ko	ko	ko	lin12dlin15koVulkolstko	2	2	2	2	2	2	n.d
25	ablated	wt	wt	wt	wt	ac-	3	3	3	3	3	3	Kimble '81
26	ablated	wt	wt	wt	ko	ac-_lstko	3	3	3	3	3	3	Berset et al. '05
27	ablated	wt	wt	ko	wt	ac-_Vulko	3	3	3	3	3	3	n.d.
28	ablated	wt	wt	ko	ko	ac-_Vulkolstko	3	3	3	3	3	3	n.d.
29	ablated	wt	ko	wt	wt	ac-_lin15ko	1\2	1\2	1\2	1\2	1\2	1\2	Sternberg & Horvitz '89
30	ablated	wt	ko	wt	ko	ac-_lin15kolstko	1	1	1	1	1	1	n.d.
31	ablated	wt	ko	ko	wt	ac-_lin15koVulko	3	3	3	3	3	3	n.d.
32	ablated	wt	ko	ko	ko	ac-_lin15koVulkolstko	3	3	3	3	3	3	n.d.
33	ablated	ko	wt	wt	wt	ac-_lin12ko	3	3	3	3	3	3	Sternberg & Horvitz '89
34	ablated	ko	wt	wt	ko	ac-_lin12kolstko	3	3	3	3	3	3	n.d.
35	ablated	ko	wt	ko	wt	ac-_Vulkolin12ko	3	3	3	3	3	3	n.d
36	ablated	ko	wt	ko	ko	ac-_lin12koVulkolstko	3	3	3	3	3	3	n.d.
37	ablated	ko	ko	wt	wt	ac-_lin15kolin12ko	1	1	1	1	1	1	Sternberg & Horvitz '89 (one animal)
38	ablated	ko	ko	wt	ko	ac-_lin12kolin15kolstko	1	1	1	1	1	1	n.d.
39	ablated	ko	ko	ko	wt	ac-_lin12kolin15koVulko	3	3	3	3	3	3	n.d.
40	ablated	ko	ko	ko	ko	ac-_lin12kolin15koVulkollstko	3	3	3	3	3	3	n.d.
41	ablated	gf	wt	wt	wt	ac-_lin12d	2	2	2	2	2	2	Sternberg & Horvitz '89
42	ablated	gf	wt	wt	ko	ac-_lin12dlstko	2	2	2	2	2	2	Berset et al. '05 (for lip-1)
43	ablated	gf	wt	ko	wt	ac-_lin12dVulko	2	2	2	2	2	2	Sternberg & Horvitz 89 (rf mutants), Han et al. '90
44	ablated	gf	wt	ko	ko	ac-_lin12dVulkolstko	2	2	2	2	2	2	n.d. (let-60dneg)
45	ablated	gf	ko	wt	wt	ac-_lin15kolin12d	1\2	1\2	1\2	1\2	1\2	1\2	Sternberg & Horvitz '89
46	ablated	gf	ko	wt	ko	ac-_lin12dlin15kolstko	1	1	1	1	1	1	n.d.
47	ablated	gf	ko	ko	wt	ac-_lin12dlin15koVulko	2	2	2	2	2	2	n.d.
48	ablated	gf	ko	ko	ko	ac-_lin12dlin15koVulkolstko	2	2	2	2	2	2	n.d

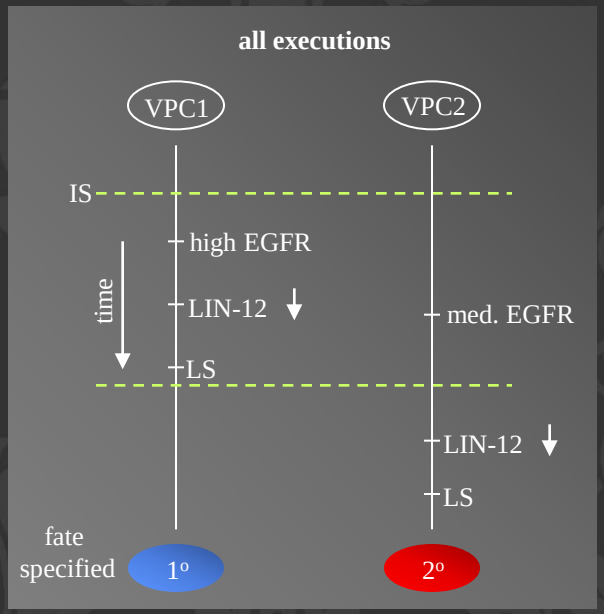
PLoS Comp. Biol. (2007) **3**(5):e92

another query:

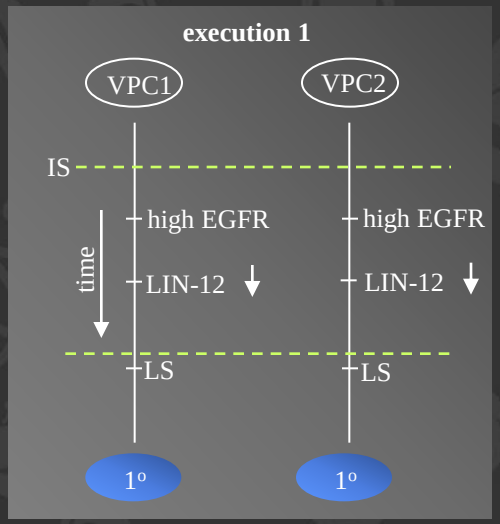
Is it possible to get an unstable fate pattern without allowing variations in the timing of the lateral signal?

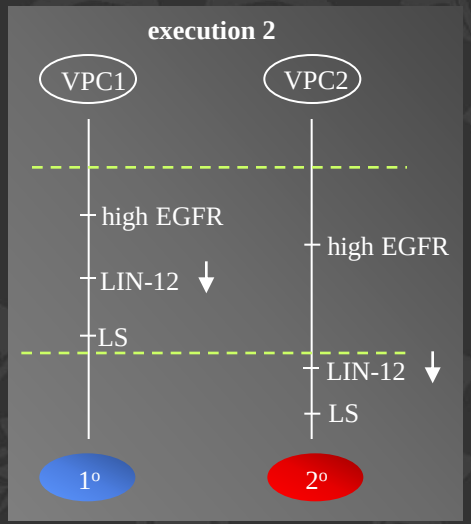
Sequence of events leading to stable and unstable fate patterns

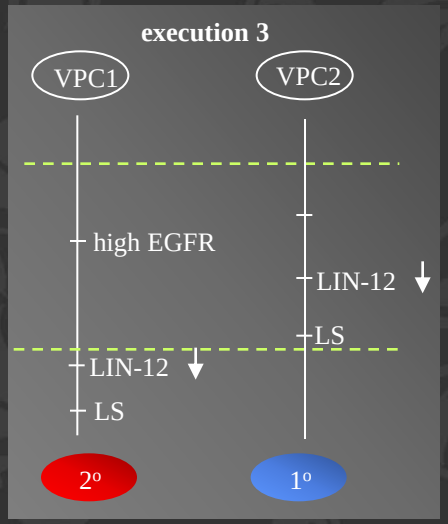
A Stable pattern



B Unstable pattern



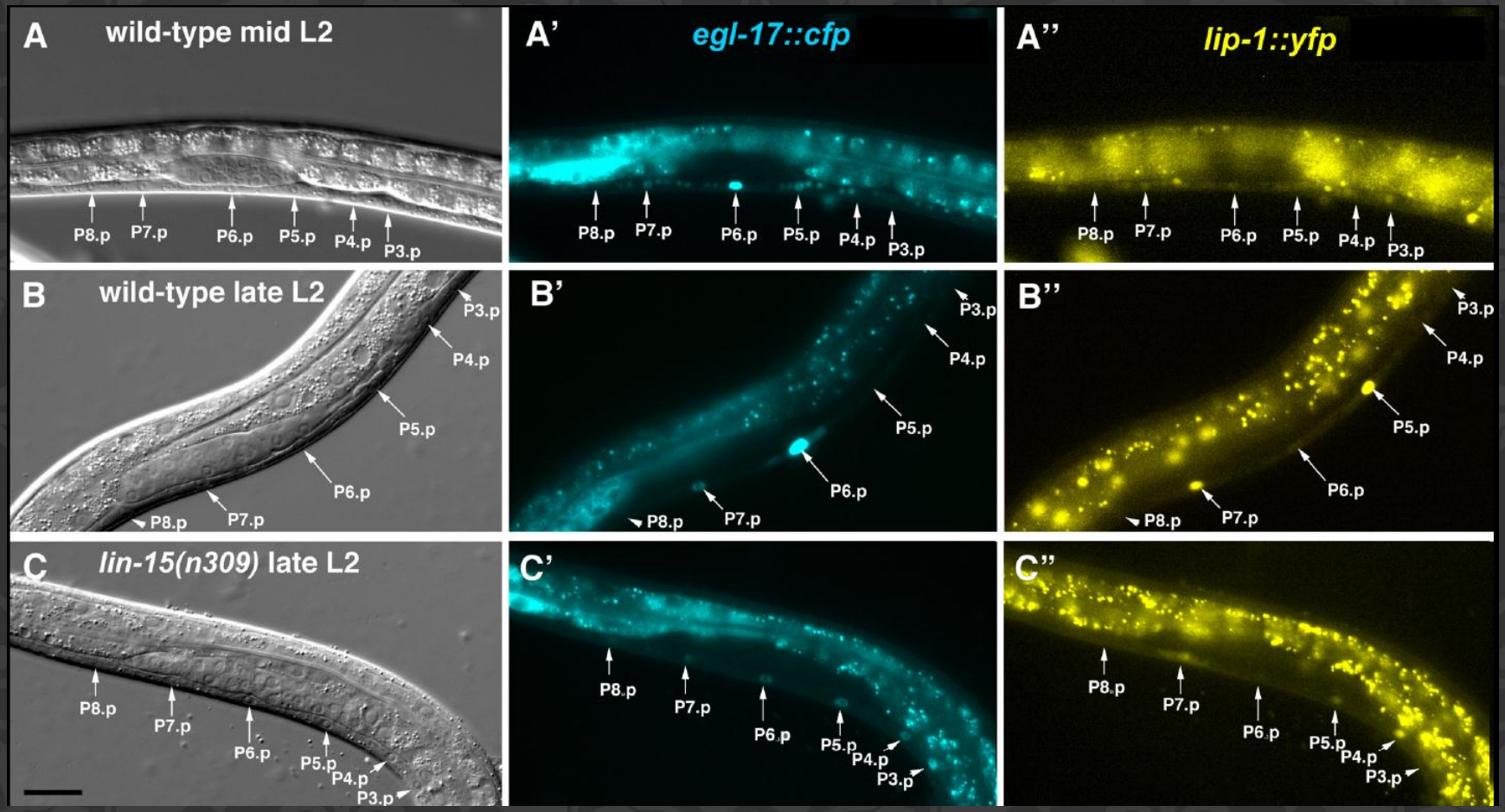




PLoS Comp. Biol. (2007) **3**(5):e92

Experimental validation of the model's predictions

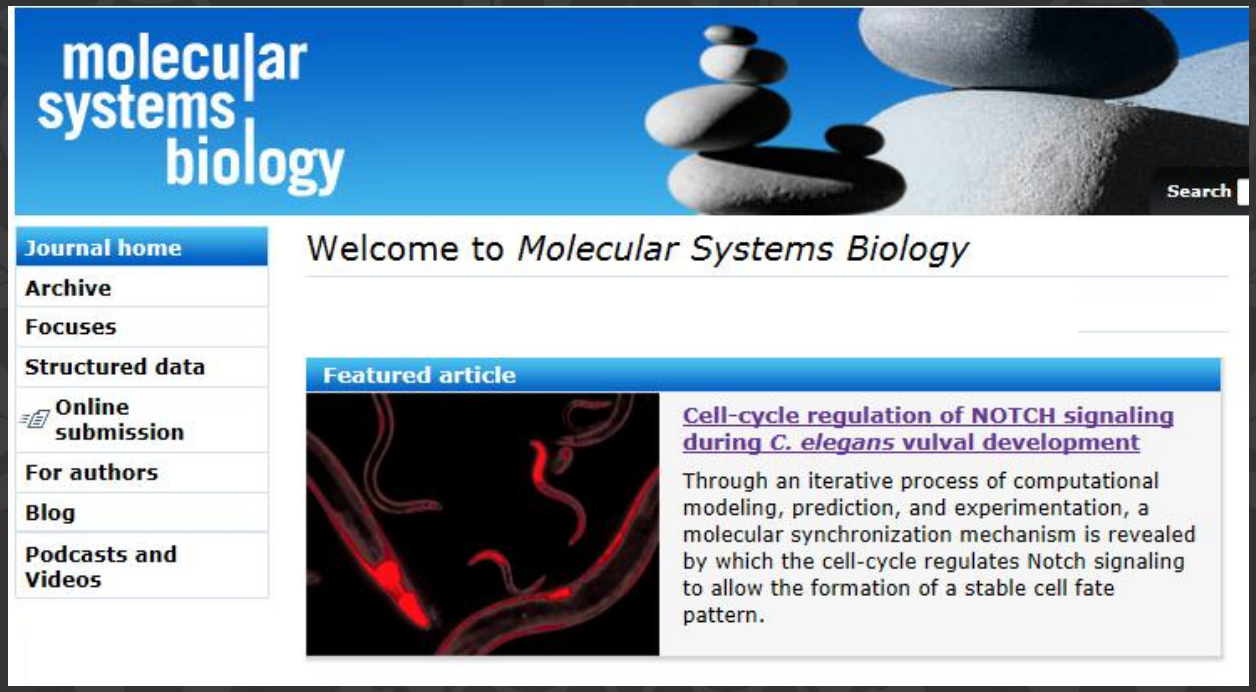
Loss of sequential induction in *lin-15* mutants



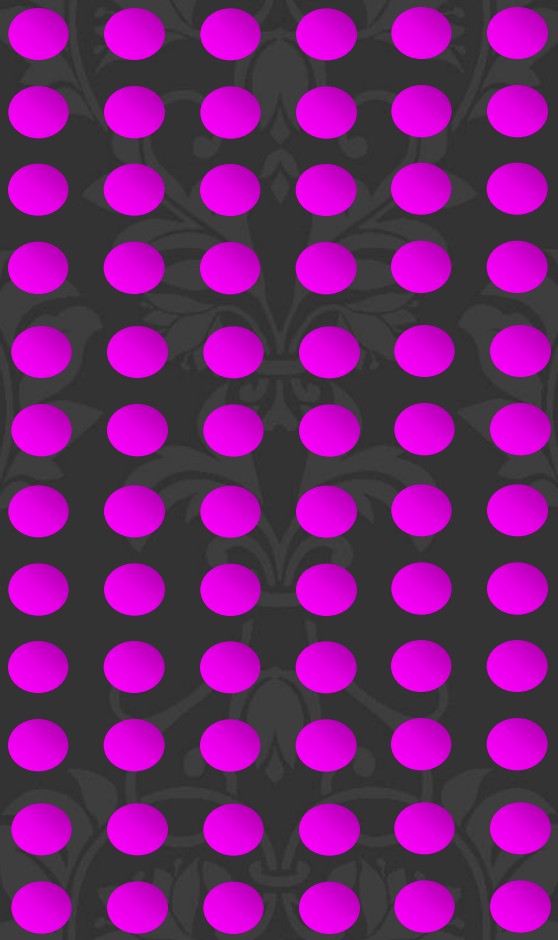
PLoS Comp. Biol. (2007) **3**(5):e92

Concurrency reveals…

a molecular synchronization mechanism



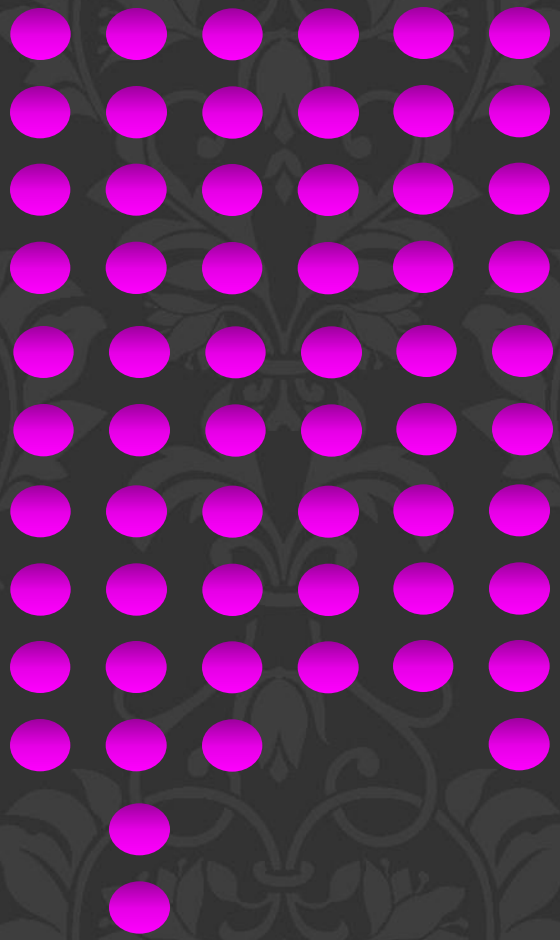
synchronous



synchronous

e.g., *lin-15(0)*

asynchronous



synchronous

e.g., *lin-15(o)*

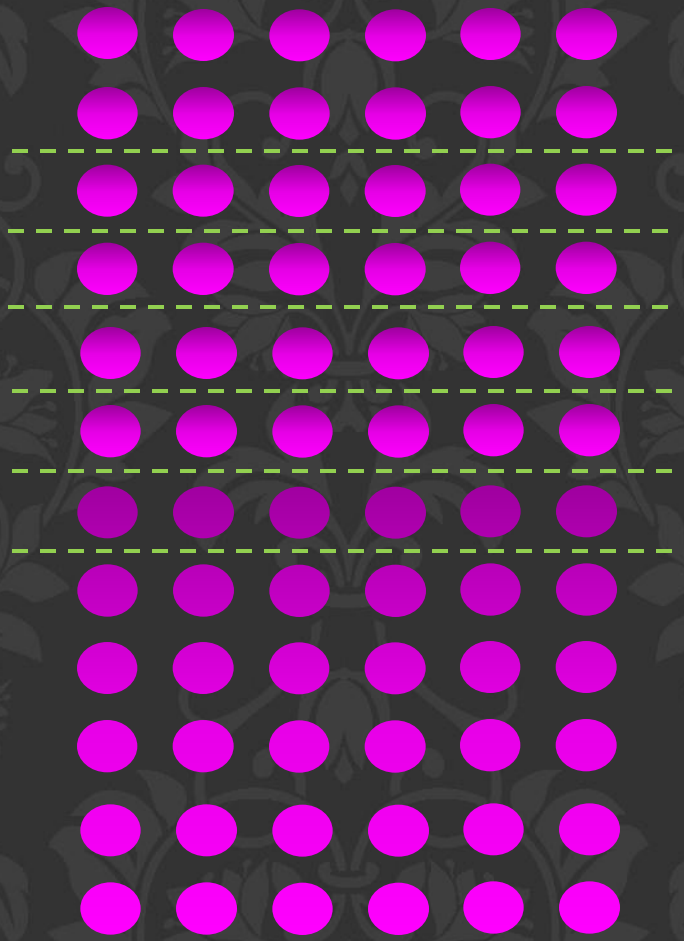
asynchronous

e.g., wt

A notion of concurrency tailored for cell-cell interactions 'bounded-asynchrony'

Fisher *et al., Formal Methods in Systems Biology; LNBI* Vol. 5054, pp. 17-32, (2008)

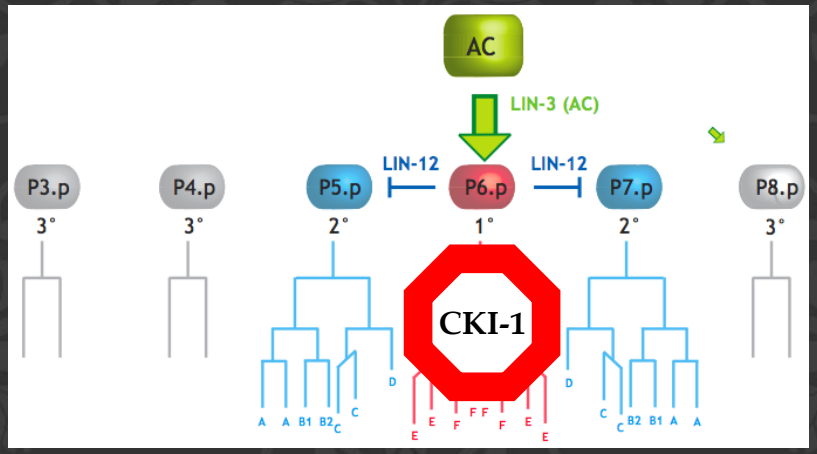
bounded asynchrony



What is the biological counterpart of the scheduler?

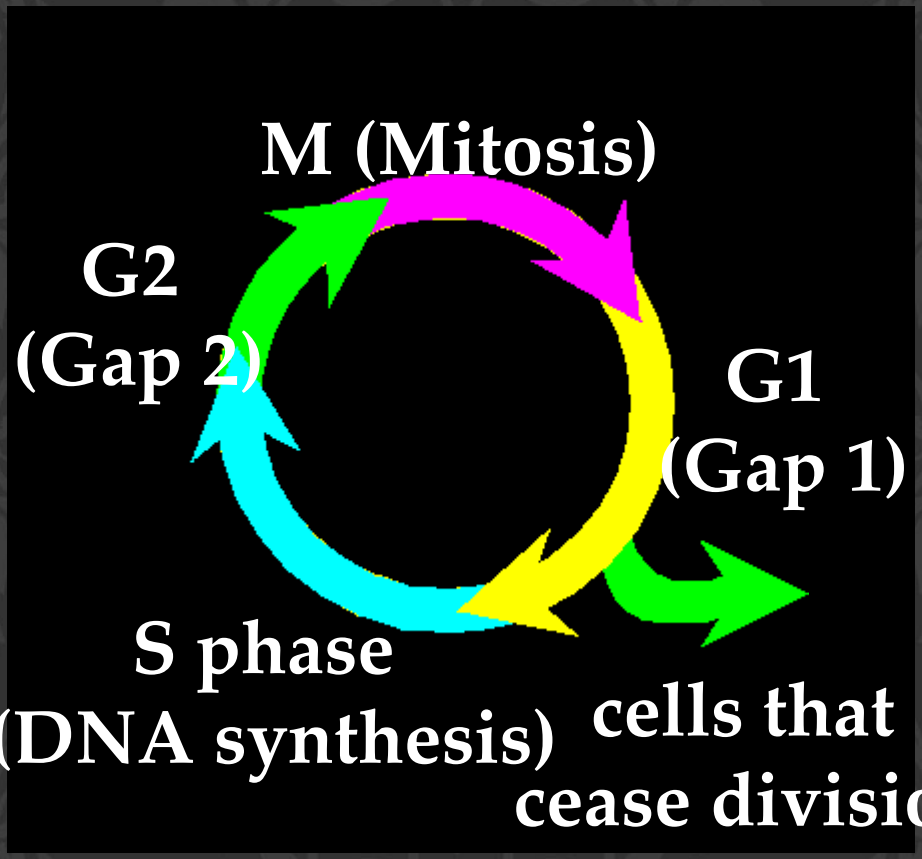
Model prediction: An impaired "scheduler" leads to affected cell fate patterning

Hypothesis: The cell cycle corresponds to the scheduler

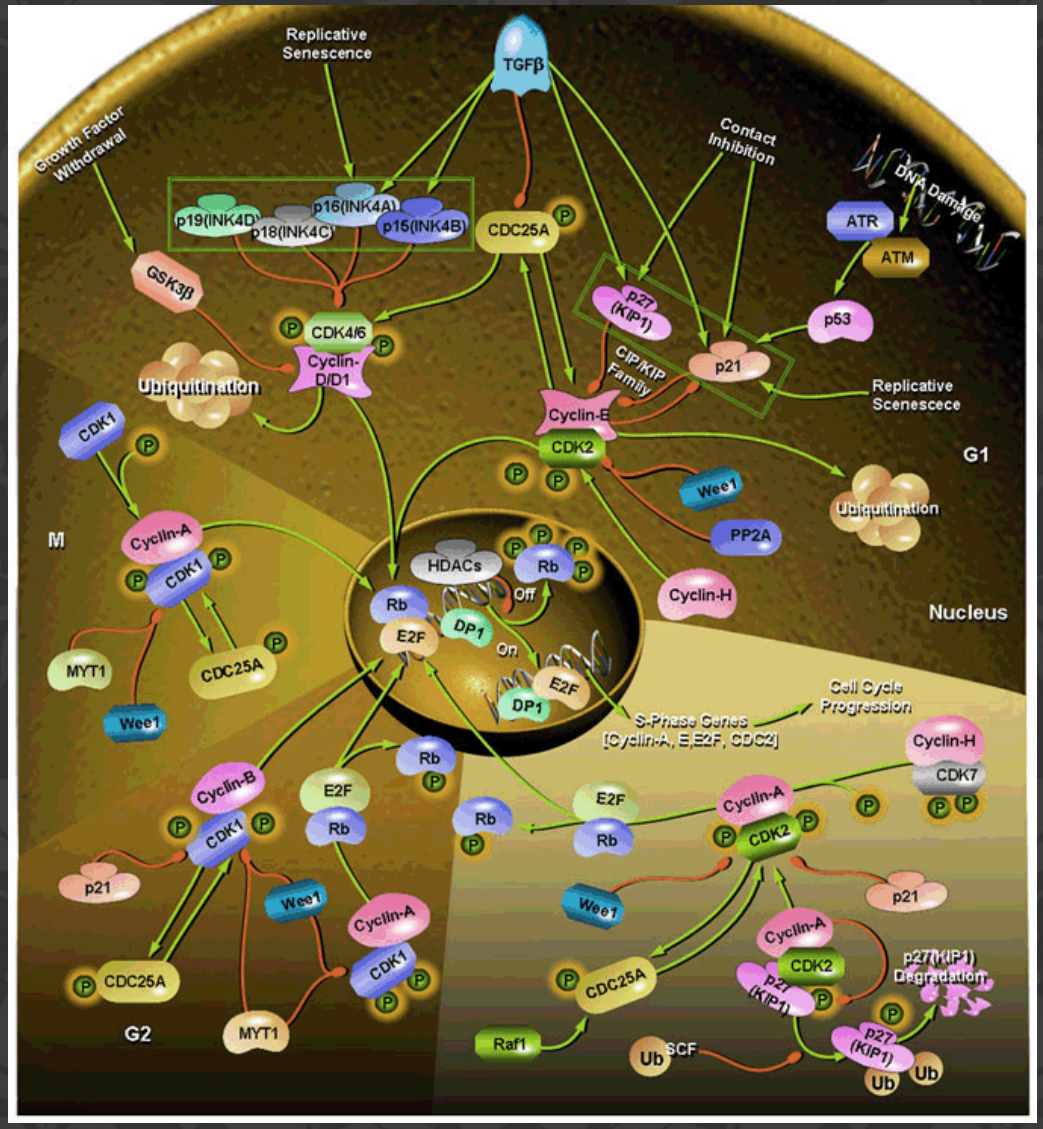


⇒ What happens to expression pattern of different cell fate markers in P6.p?

Cell-cycle


M (Mitosis)
G2
(Gap 2)
G1
(Gap 1)
S phase
(DNA synthesis)
cells that
cease division

Cell-cycle regulation



Cell-cycle Regulation of Cancer Signalling


Alex Hajnal


Stefanie Nusser

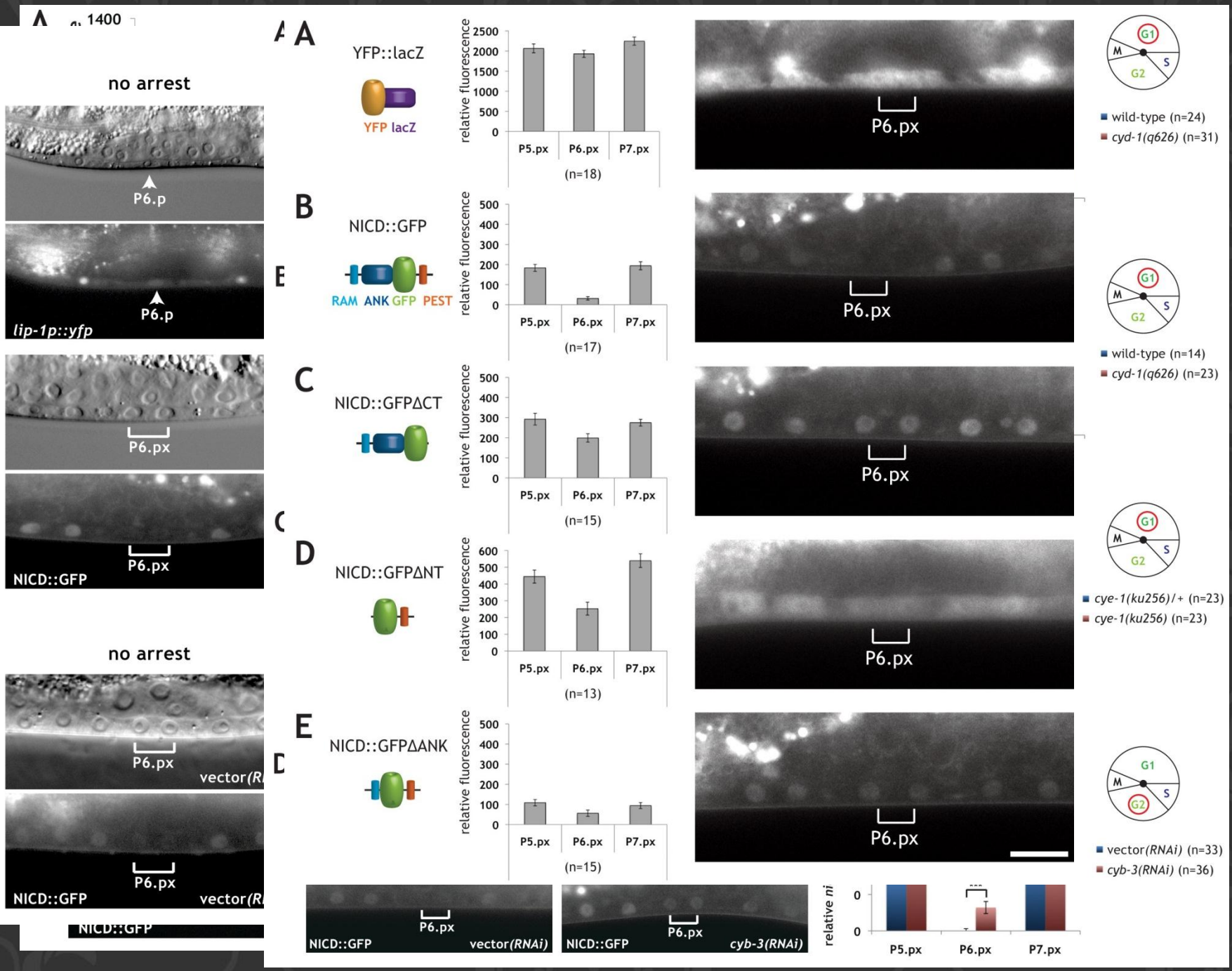

Ivo Rimann


Magdalene Adamczyk

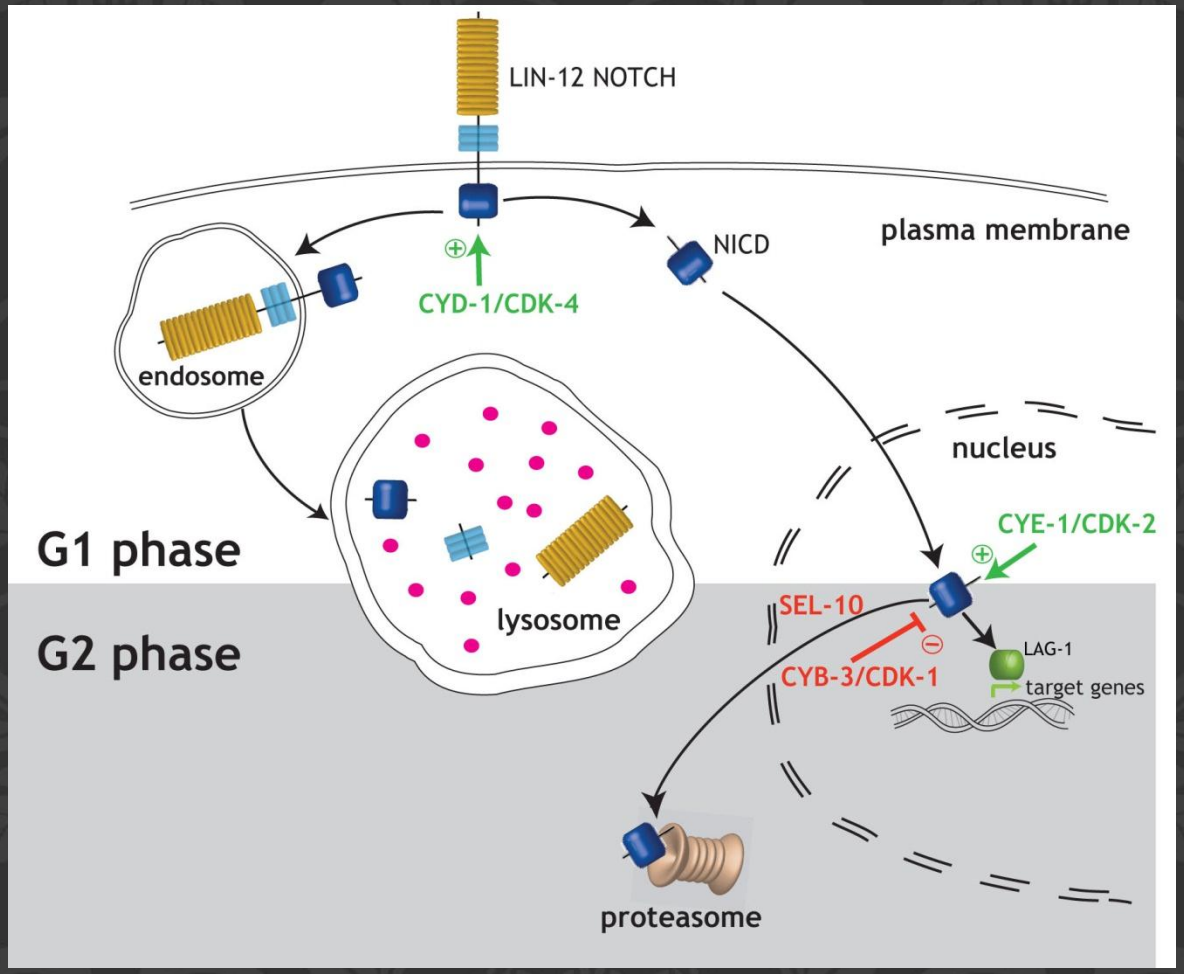
Zurich University


Antje Beyer
University of
Cambridge

Nusser-Stein *et al.* *Molecular Systems Biology* **8**:618, 2012

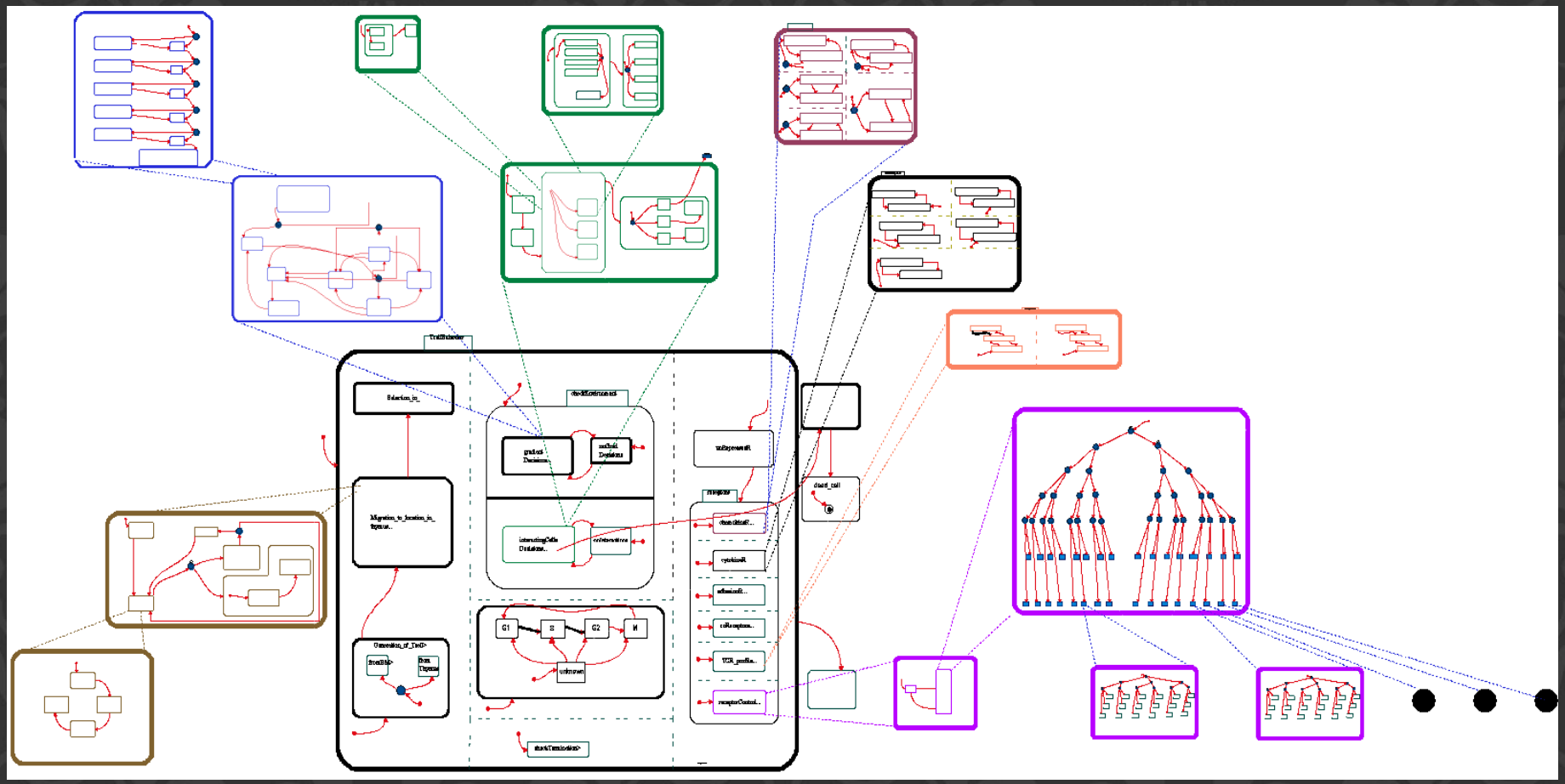

no arrest
A
P6.p
P6.p
lip-1p::yfp
B
P6.px
P6.px
NICD::GFP
no arrest
C
P6.px
vector(R
P6.px
NICD::GFP
vector(R
NICD::GFP
A
YFP::lacZ
YFP lacZ
relative fluorescence
2500
2000
1500
1000
500
0
P5.px
P6.px
P7.px
(n=18)
P6.px
G1
M
S
G2
wild-type (n=24)
cyd-1(q626) (n=31)
B
NICD::GFP
RAM ANK GFP PEST
relative fluorescence
500
400
300
200
100
0
P5.px
P6.px
P7.px
(n=17)
P6.px
wild-type (n=14)
cyd-1(q626) (n=23)
C
NICD::GFPΔCT
relative fluorescence
500
400
300
200
100
0
P5.px
P6.px
P7.px
(n=15)
P6.px
D
NICD::GFPΔNT
relative fluorescence
600
500
400
300
200
100
0
P5.px
P6.px
P7.px
(n=13)
P6.px
cye-1(ku256)/+ (n=23)
cye-1(ku256) (n=23)
E
NICD::GFPΔANK
relative fluorescence
500
400
300
200
100
0
P5.px
P6.px
P7.px
(n=15)
P6.px
vector(RNAi) (n=33)
cyb-3(RNAi) (n=36)
P6.px
NICD::GFP
vector(RNAi)
P6.px
NICD::GFP
cyb-3(RNAi)
relative ni
0
0
P5.px
P6.px
P7.px

Model for Notch Regulation by the Cell Cycle Machinery



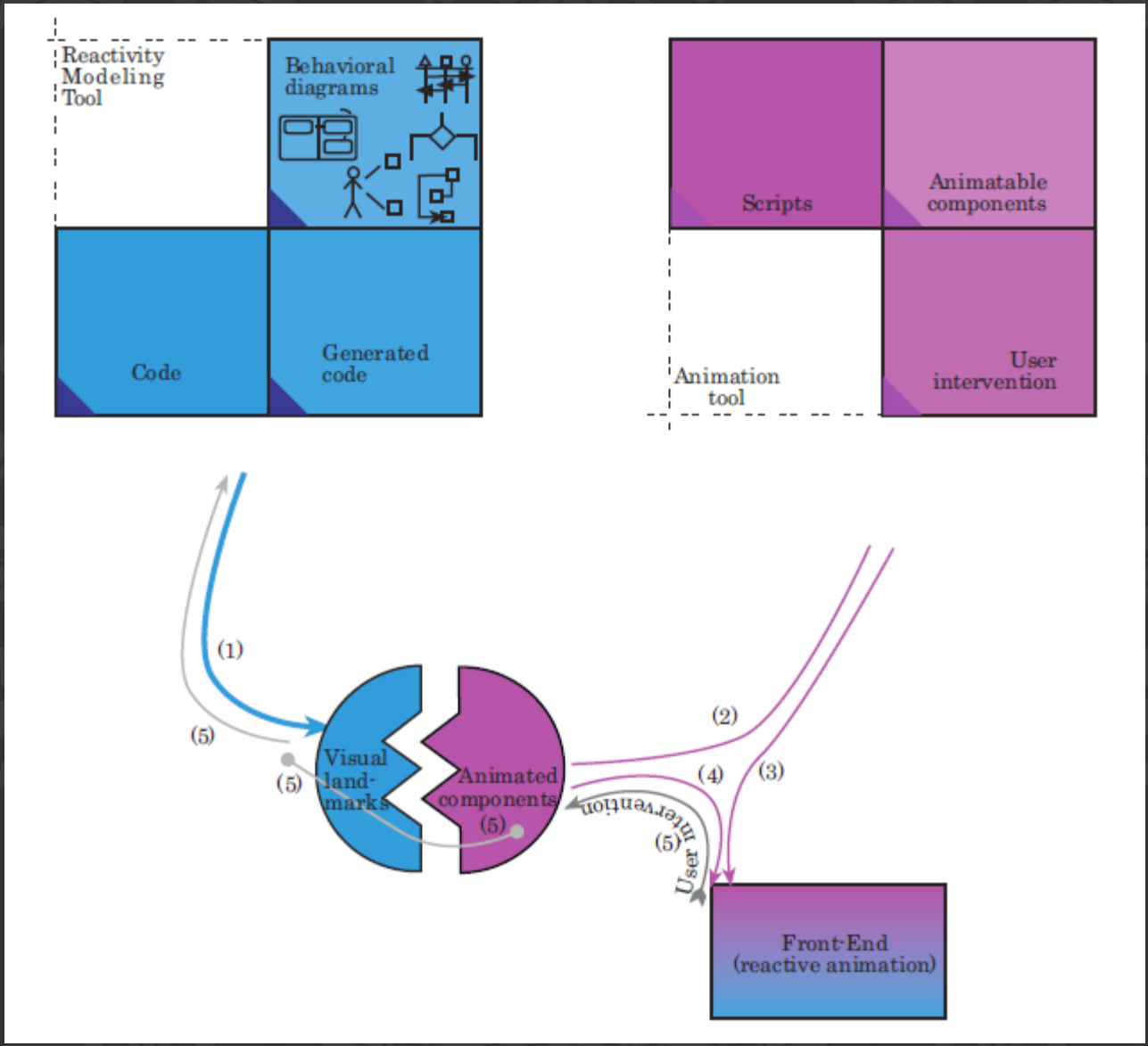
Nusser-Stein *et al.* *Molecular Systems Biology* **8**:618, 2012

Statechart of a T cell in the thymus



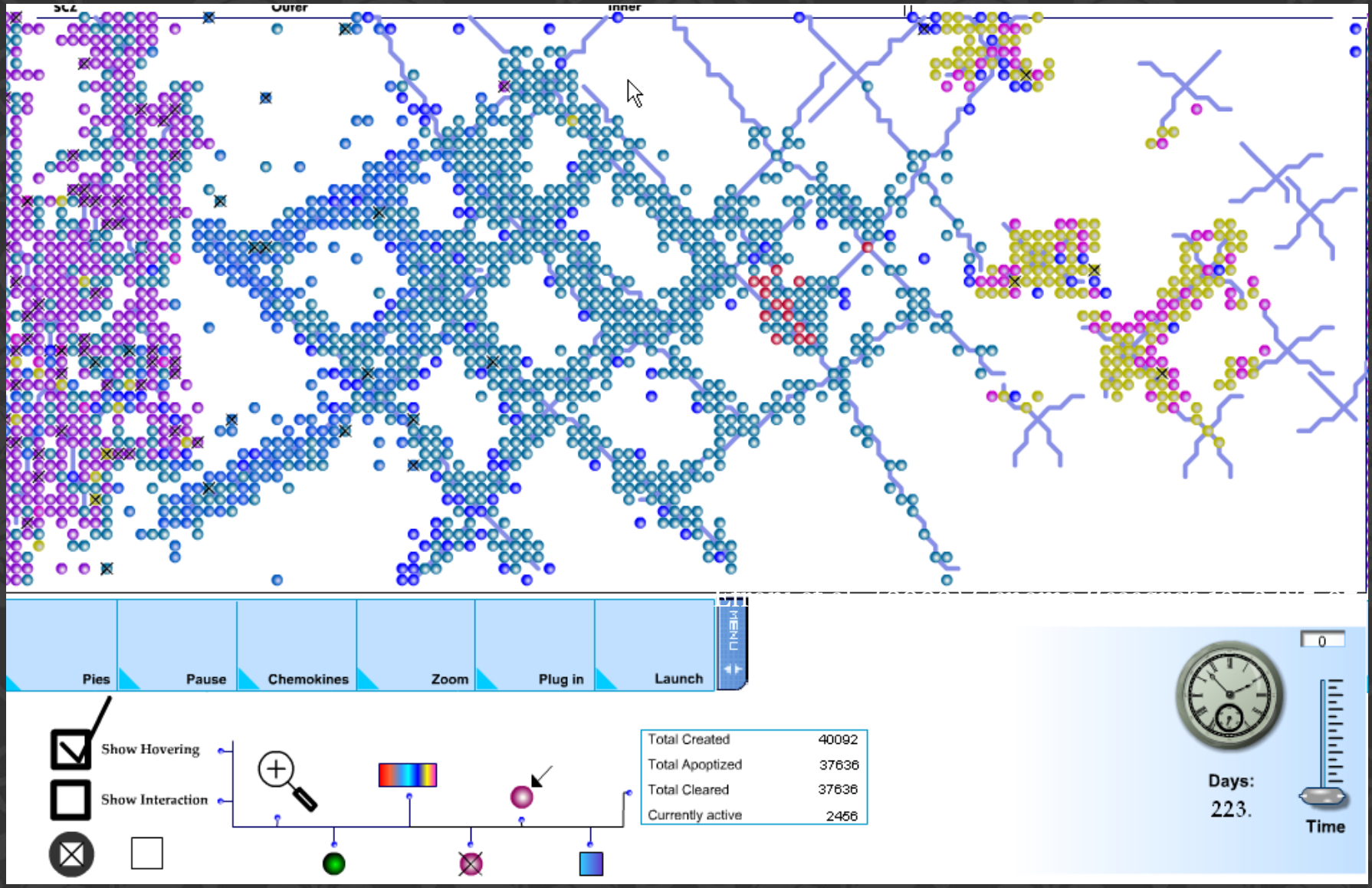
Efroni et al., (2003) *Genome Research* 13: 2485-97

Reactive Animation (Harel, Efroni & Cohen '03)

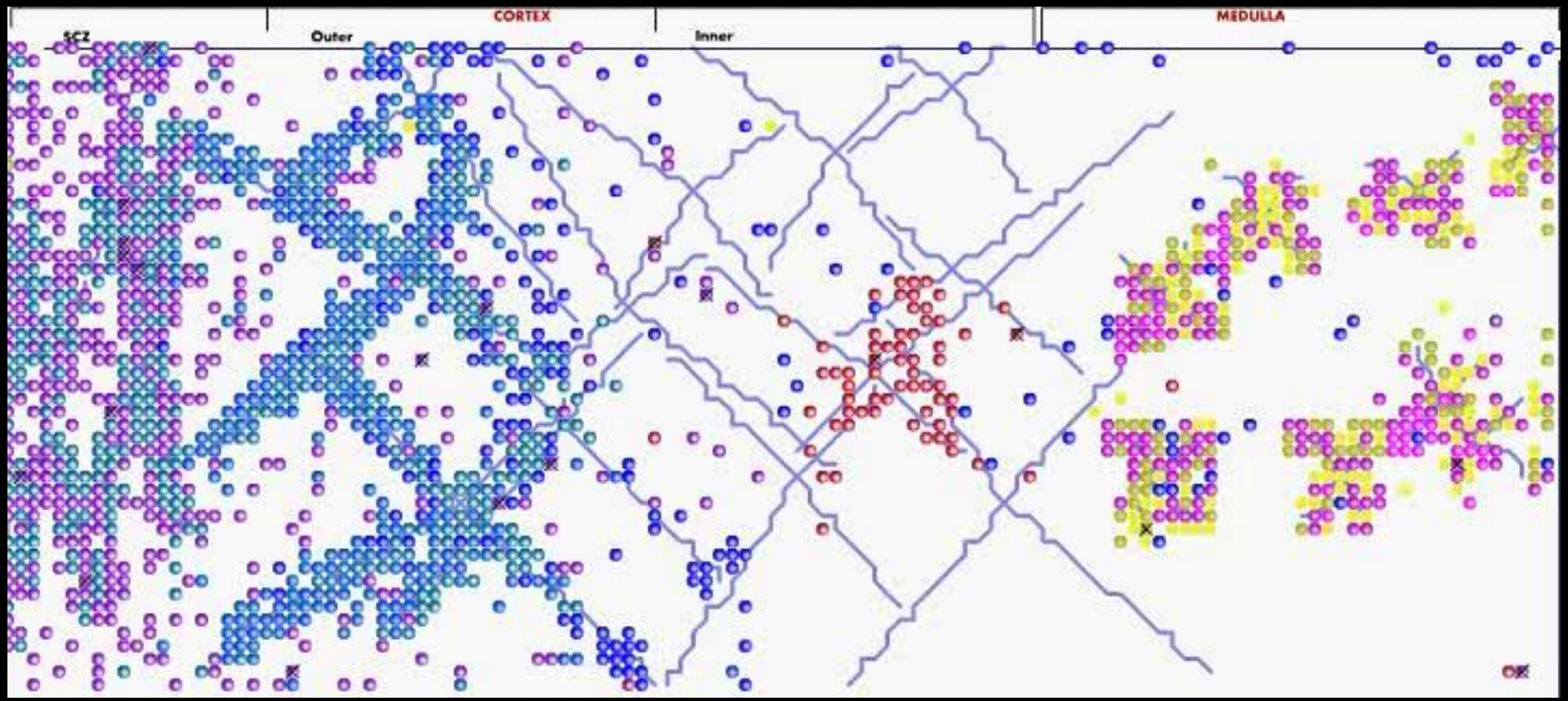


Lecture Notes in Computer Science, 2852: 136-153, 2003

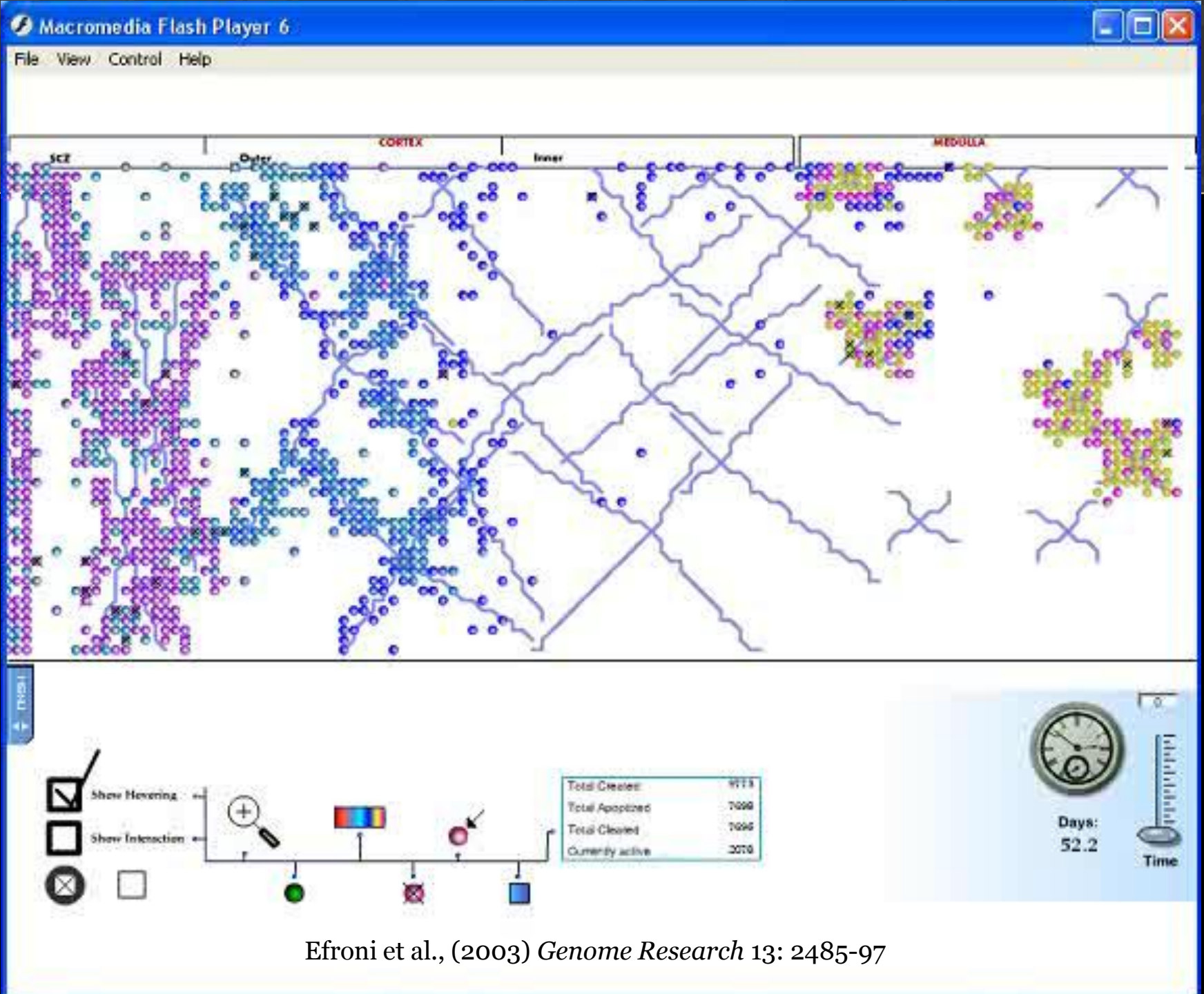
Reactive Animation (Harel, Efroni)



Efroni et al., (2003) *Genome Research* 13: 2485-97

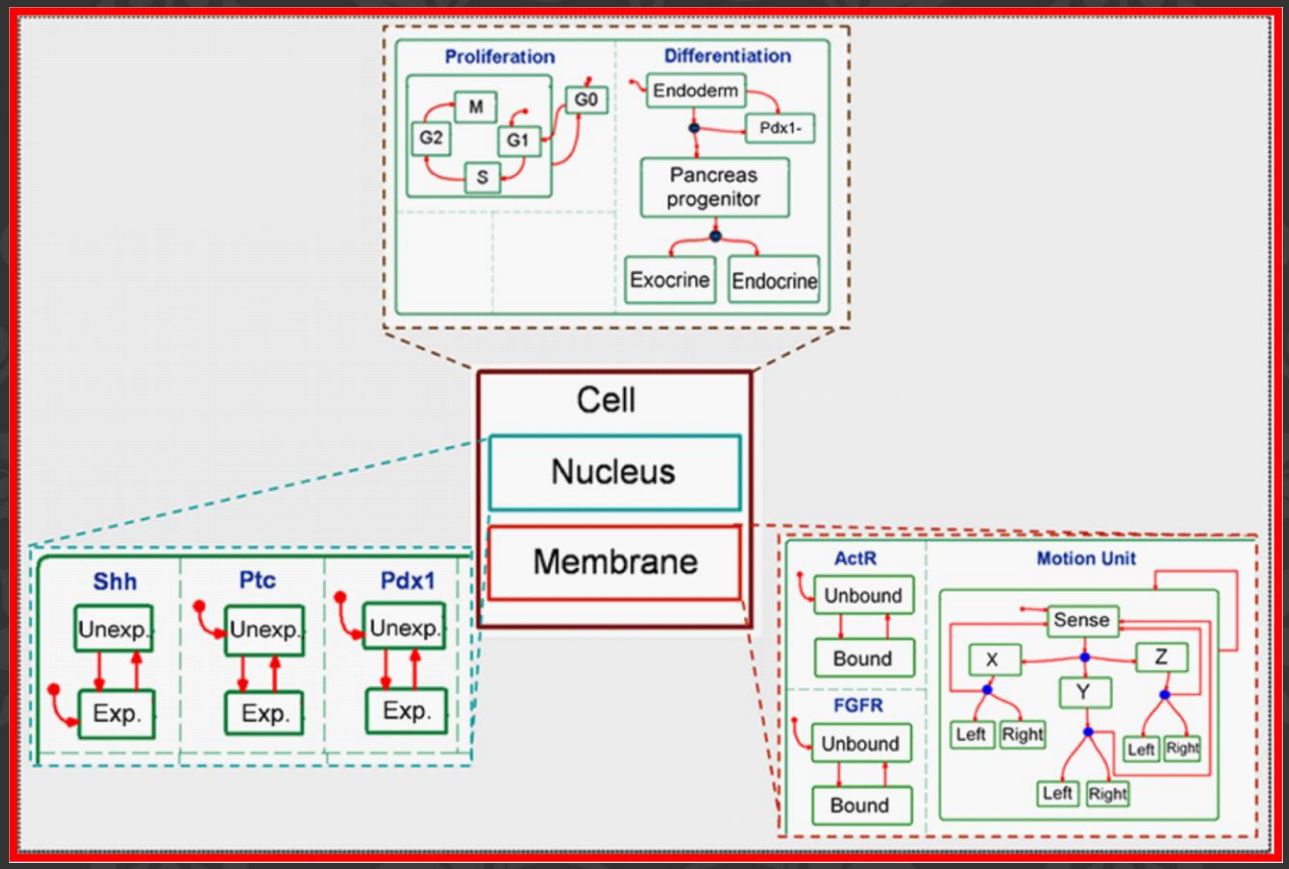


Efroni et al., (2003) *Genome Research* 13: 2485-97



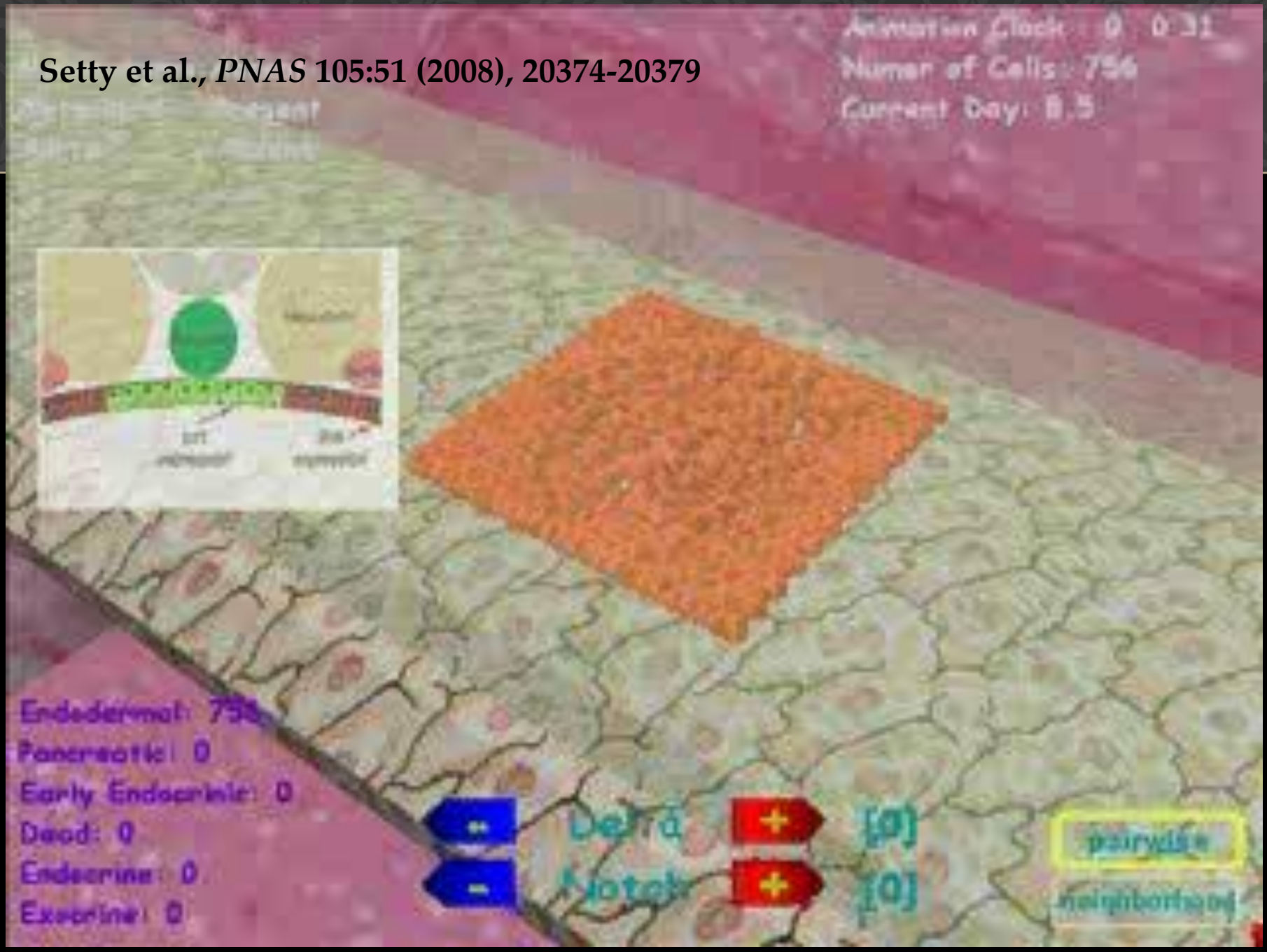
Efroni et al., (2003) *Genome Research* 13: 2485-97

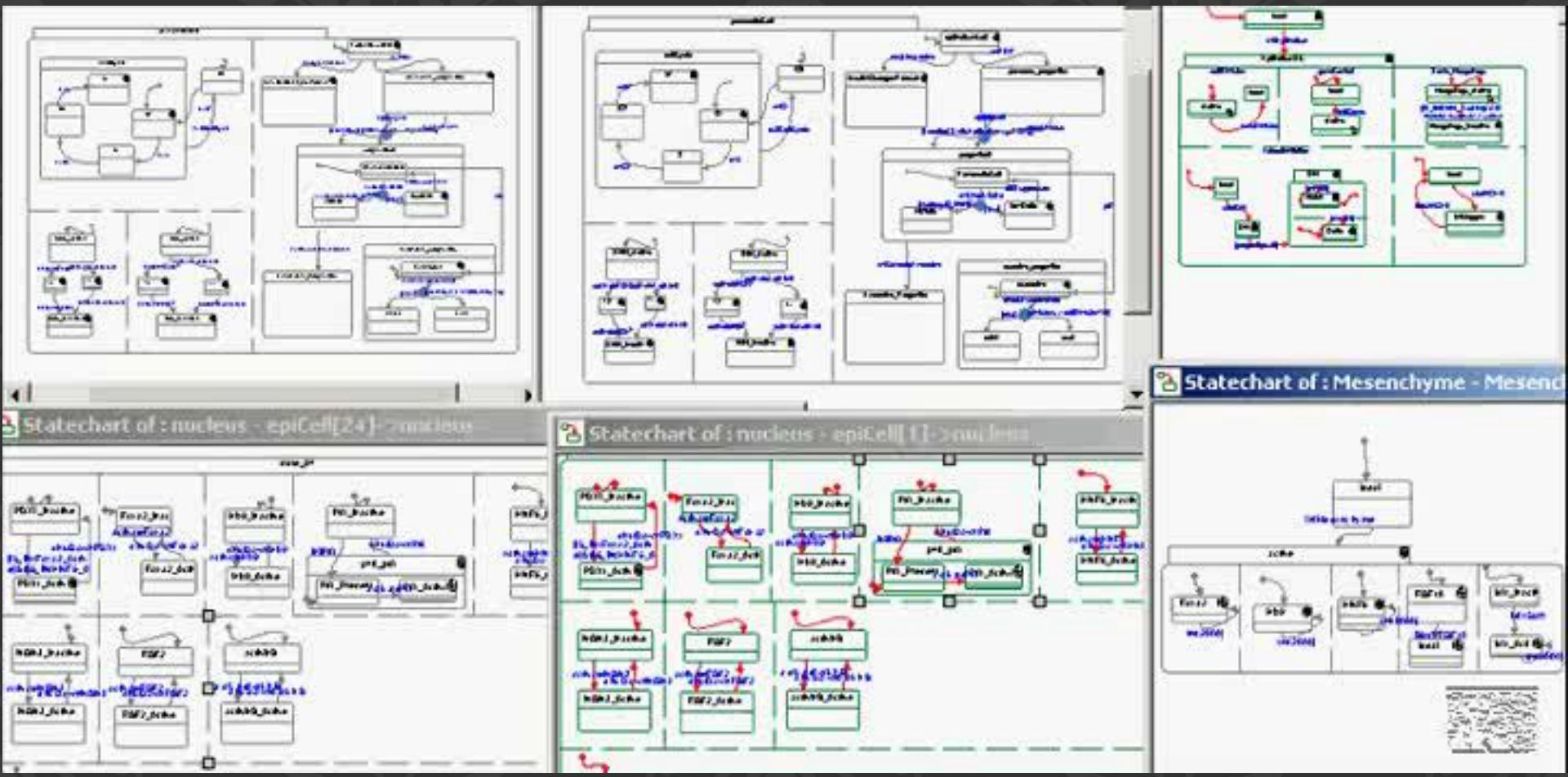
Statechart of pancreas (Harel, Setty)



Harel et al., *Electronic Notes in Theoretical Computer Science* 194 (2008)

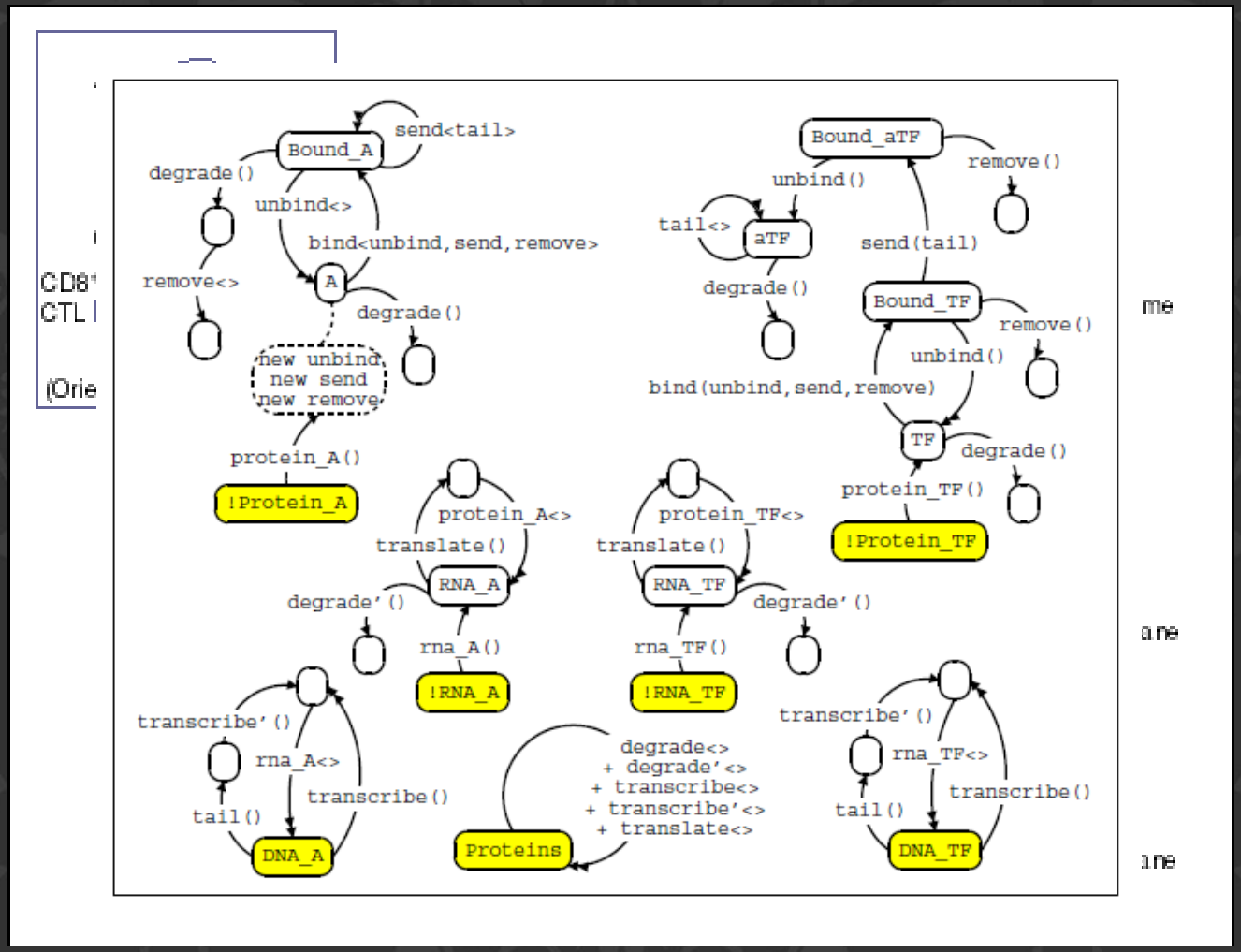
Setty et al., *PNAS* 105:51 (2008), 20374-20379





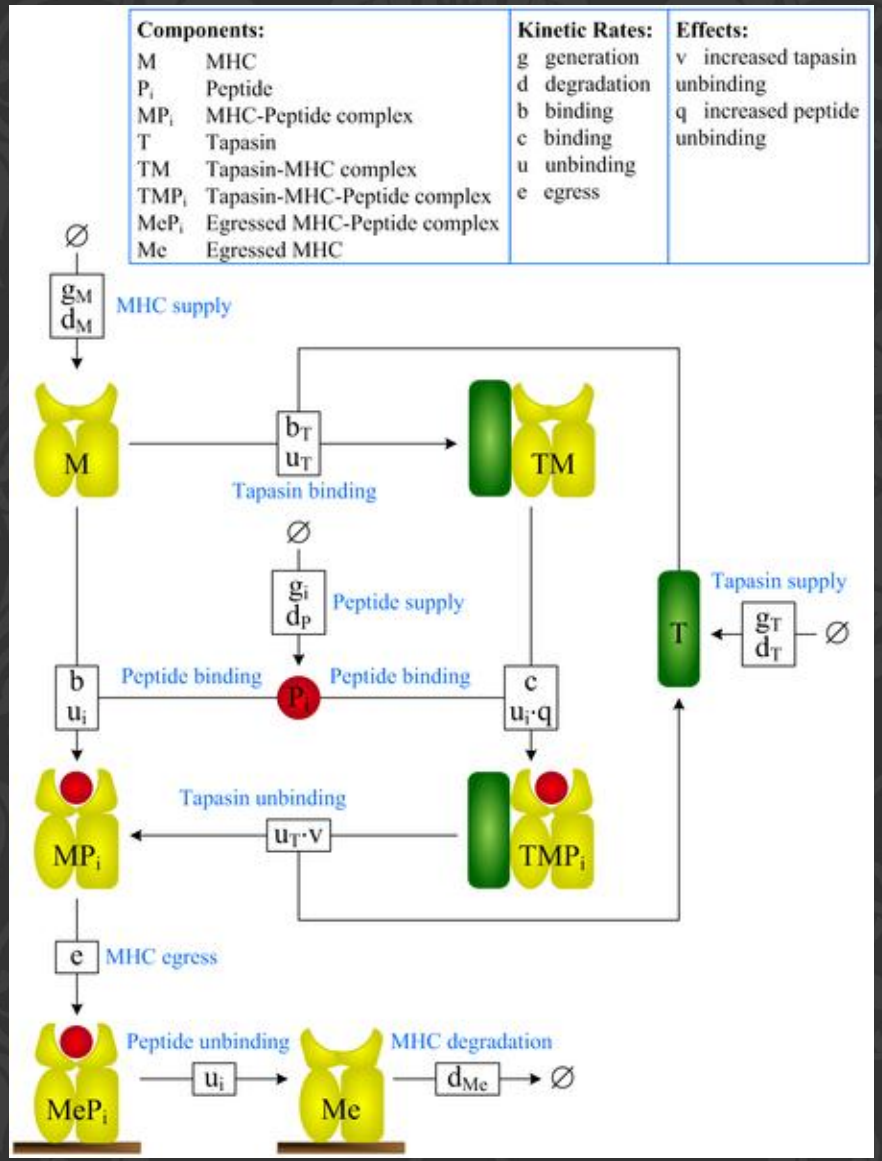
Setty et al., *PNAS* 105:51 (2008), 20374-20379

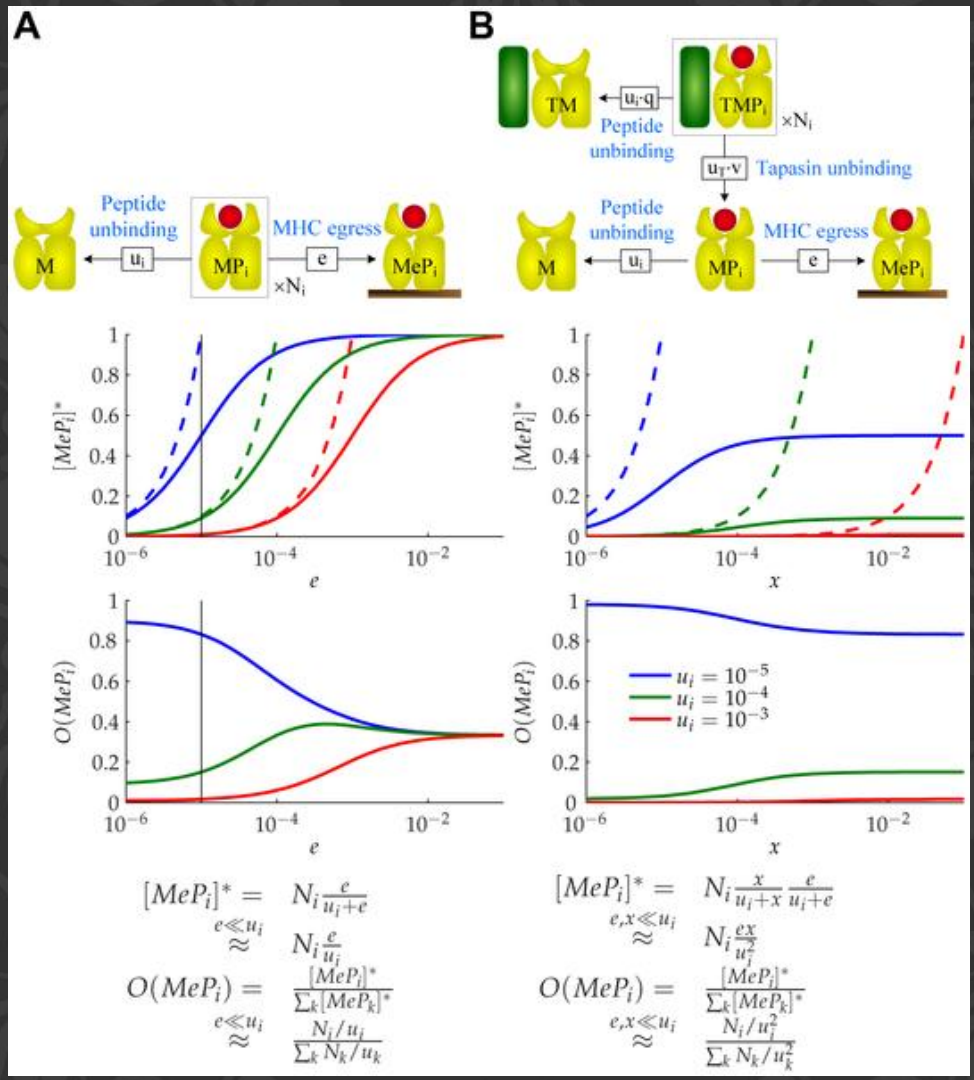
Modelling biochemical networks using Process Calculi



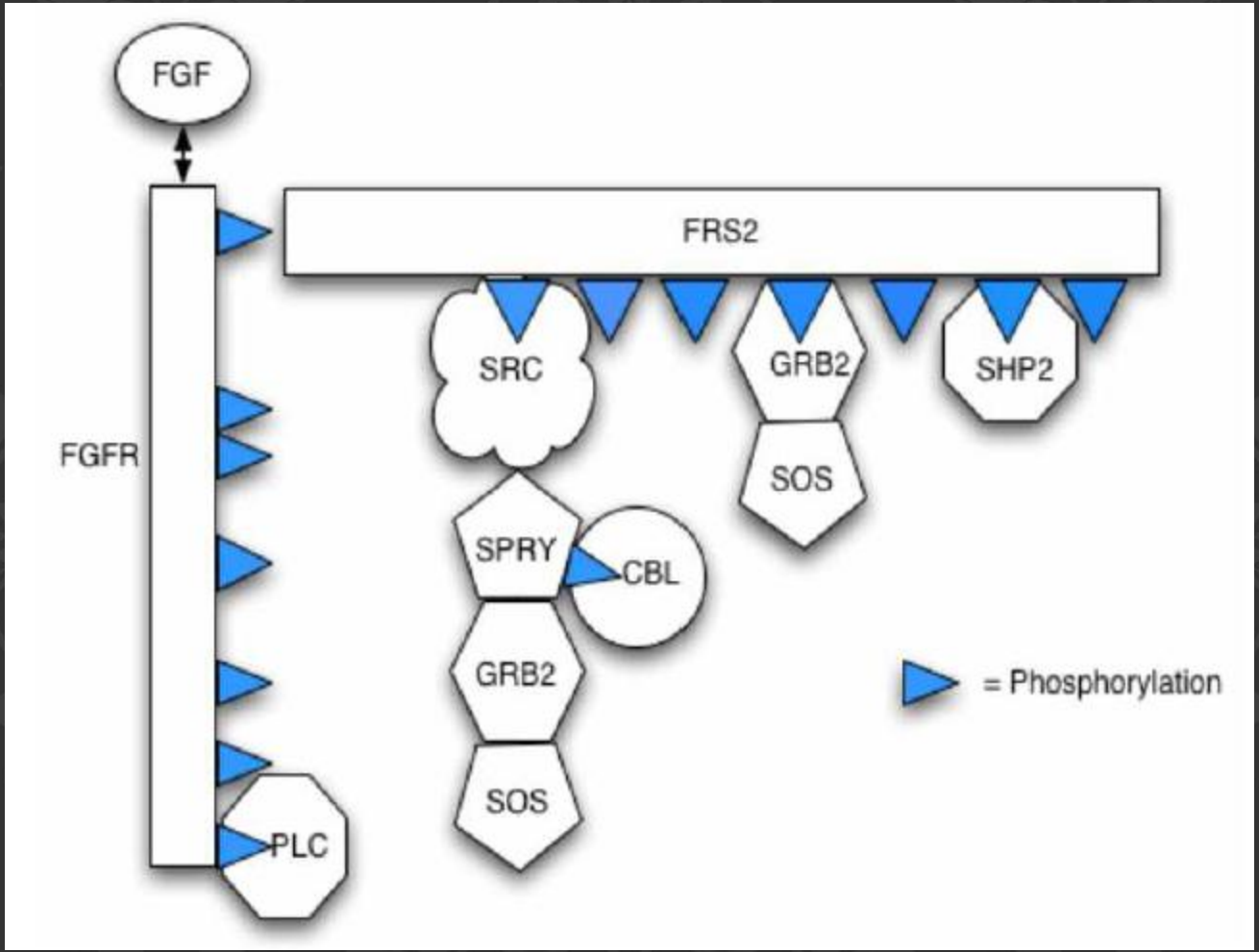
Modelling modulation of immune signalling

Dalchau, Phillips, Cardelli, et al. *PLoS Comp Biol* 7(10): e1002144 (2011)

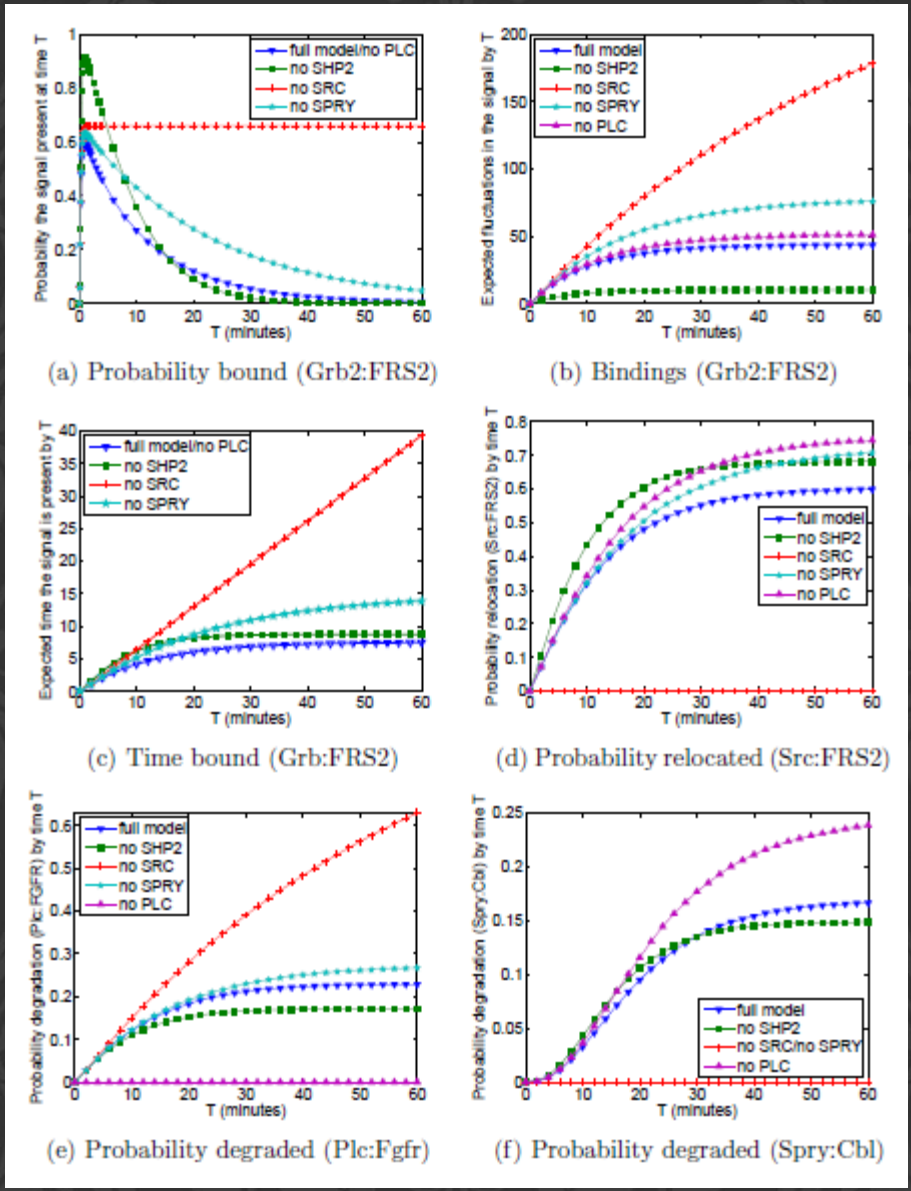




Probabilistic Model Checking of FGF Pathway

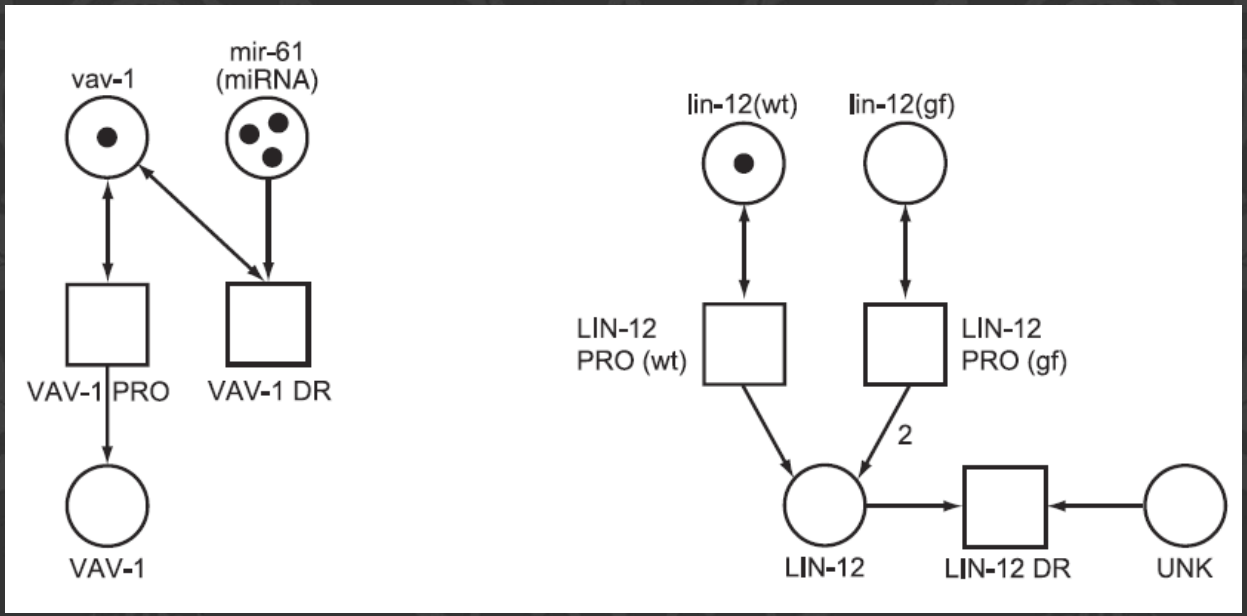


Kwiatkowska et al., *Theoretical Computer Science* 391(3): 239-257, *2008*

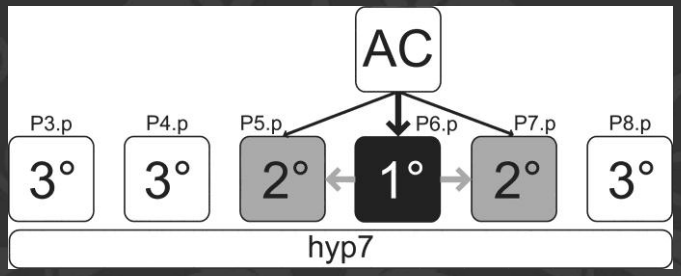


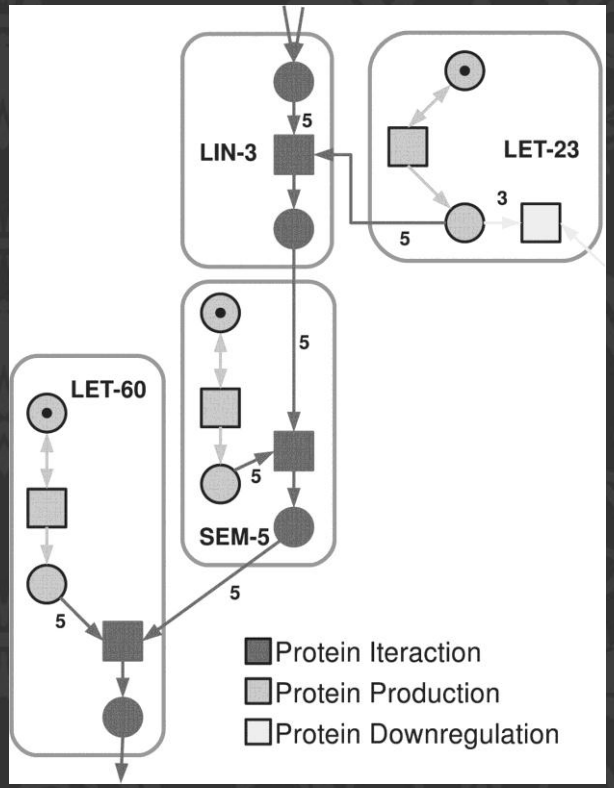
Heath, Kwiatkowska et al., *Theoretical Computer Science* 391(3): 239-257, *2008*

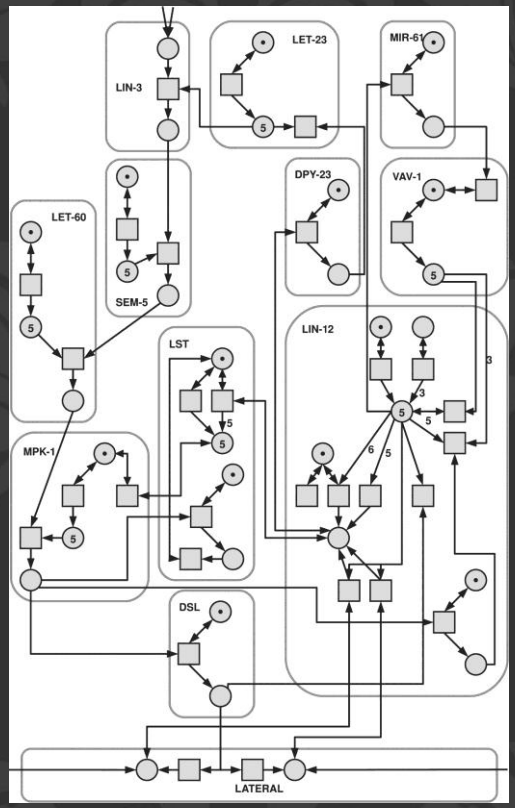
Modelling signal transduction pathways Using Petri Nets

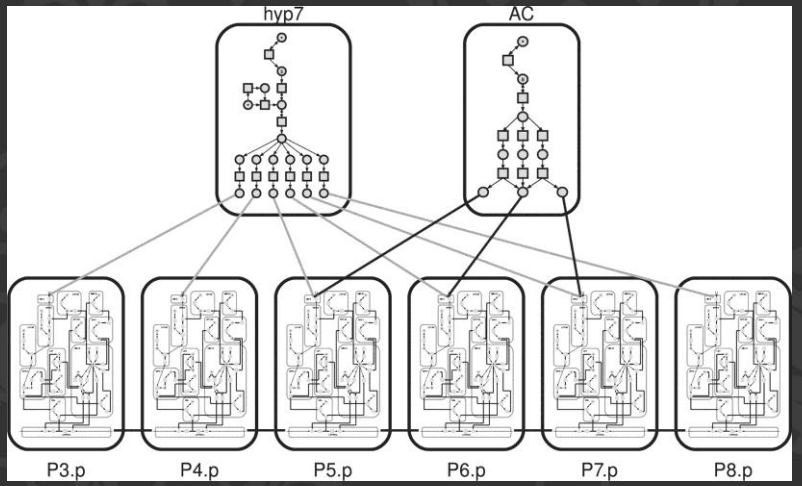


Modelling C. elegans vulval development with Petri nets



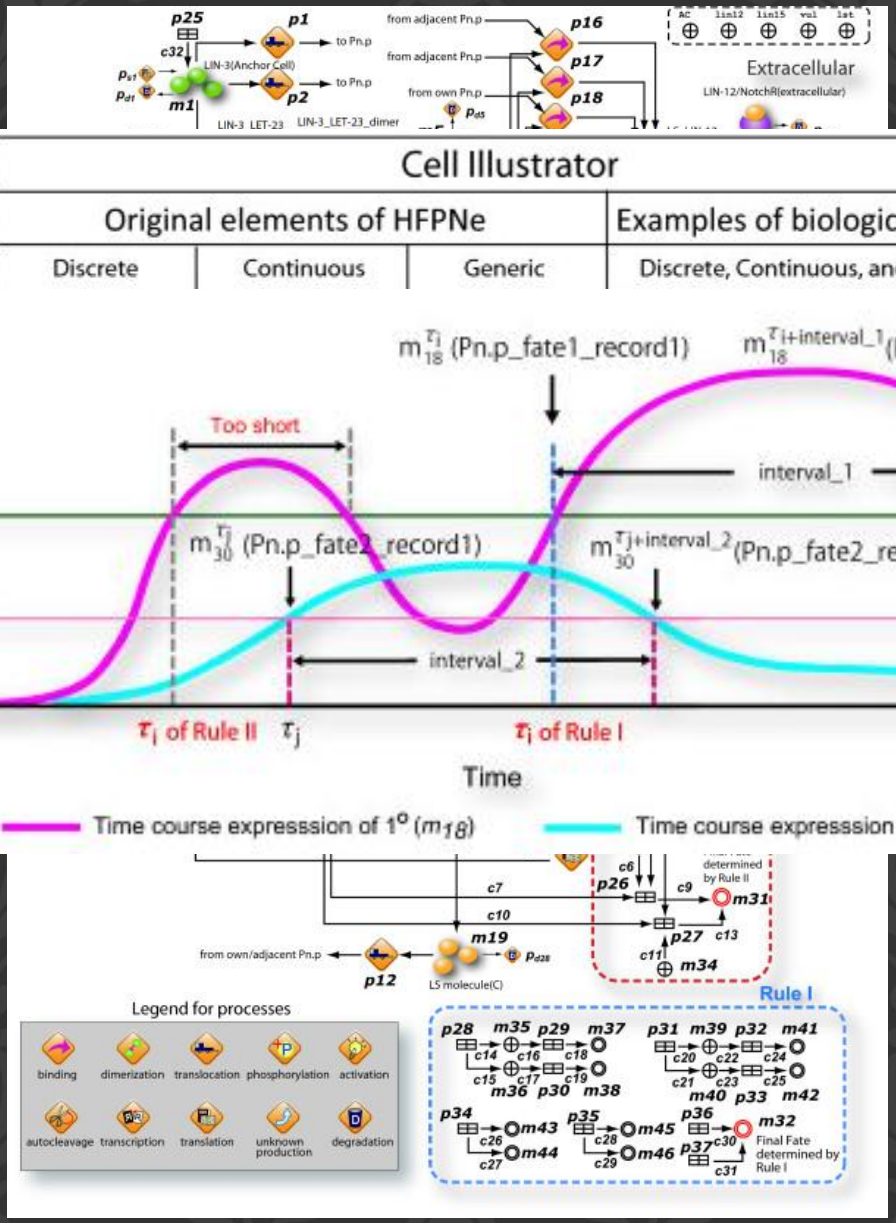






Bonzanni *et al*. *Bioinformatics* 25:2049-2056, 2009

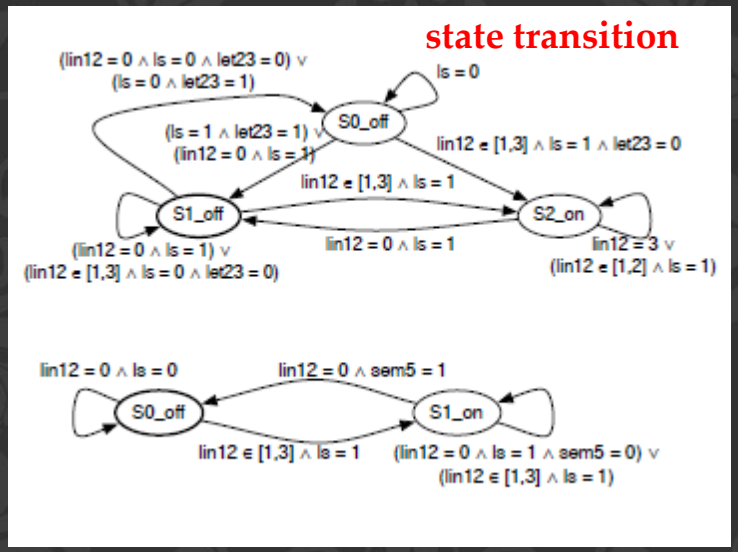
Modelling C. elegans vulval development with hybrid functional Petri nets

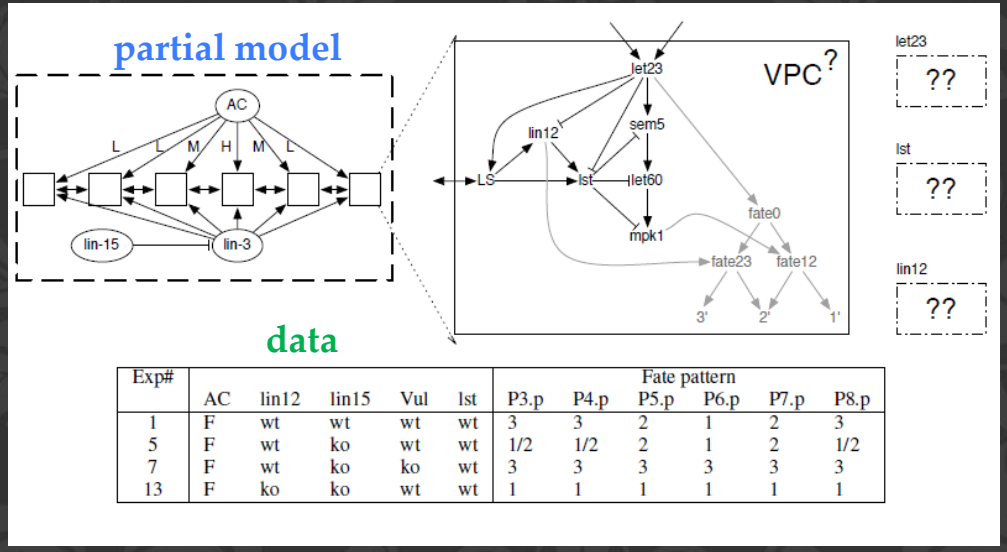


Li, Nagasaki, Ueno & Miyano, *BMC Systems Biology* 2009, 3:42

Synthesis of Biological Models from Mutation Experiments

Koksal, Pu, Srivastava, Bodik et al. *POPL '13*





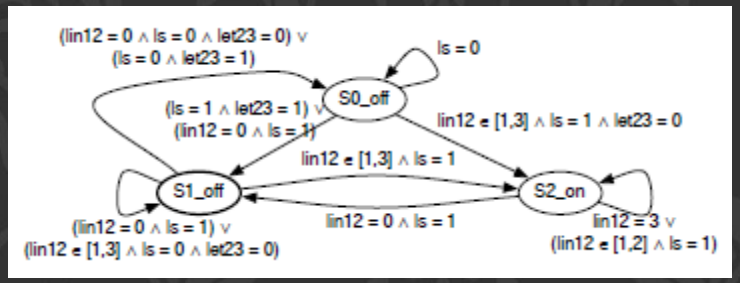
data

Exp#	AC	lin12	lin15	Vul	lst	Fate pattern P3.p	P4.p	P5.p	P6.p	P7.p	P8.p
1	F	wt	wt	wt	wt	3	3	2	1	2	3
5	F	wt	ko	wt	wt	1/2	1/2	2	1	2	1/2
7	F	wt	ko	ko	wt	3	3	3	3	3	3
13	F	ko	ko	wt	wt	1	1	1	1	1	1

synthesis

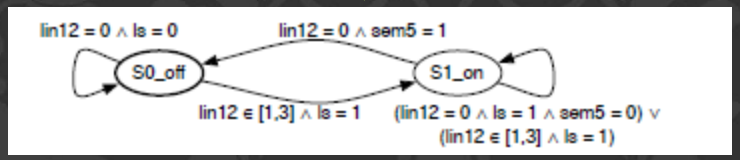
Koksal, Pu, Srivastava, Bodik et al. *POPL '13*

Koksal, Pu, Srivastava, Bodik et al. *POPL '13*



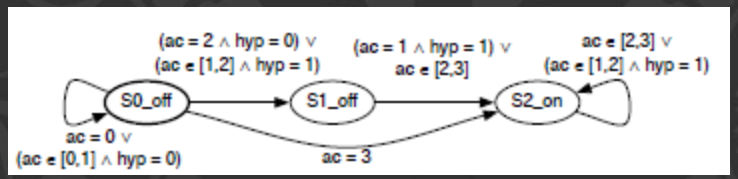
synthesis

experiments

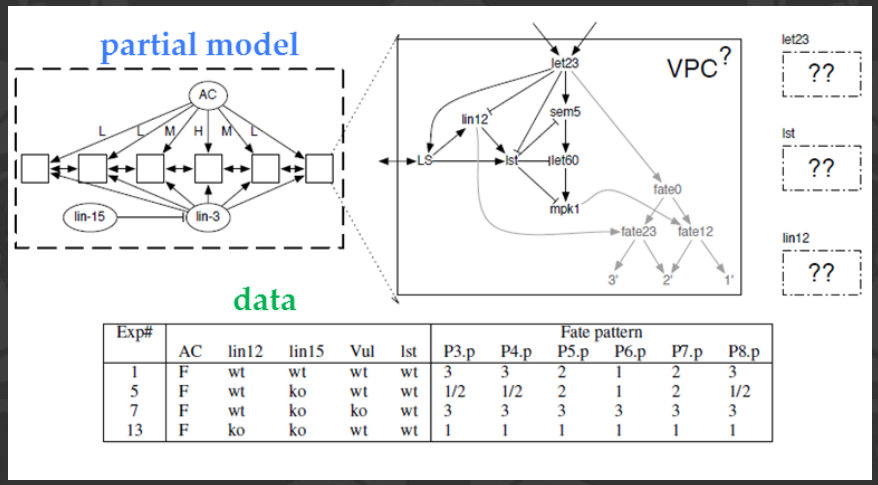


synthesis

experiments



synthesis

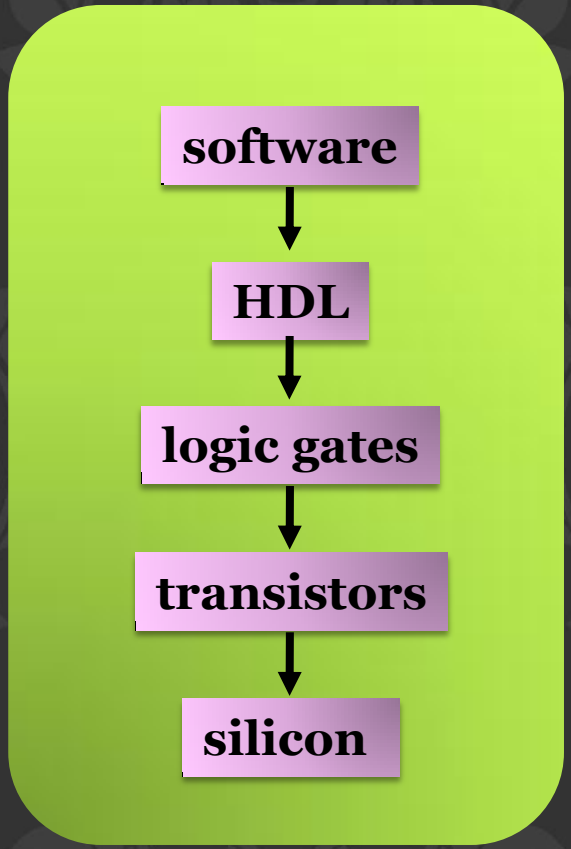


Exp#	AC	lin12	lin15	Vul	lst	Fate pattern P3.p	P4.p	P5.p	P6.p	P7.p	P8.p
1	F	wt	wt	wt	wt	3	3	2	1	2	3
5	F	wt	ko	wt	wt	1/2	1/2	2	1	2	1/2
7	F	wt	ko	ko	wt	3	3	3	3	3	3
13	F	ko	ko	wt	wt	1	1	1	1	1	1

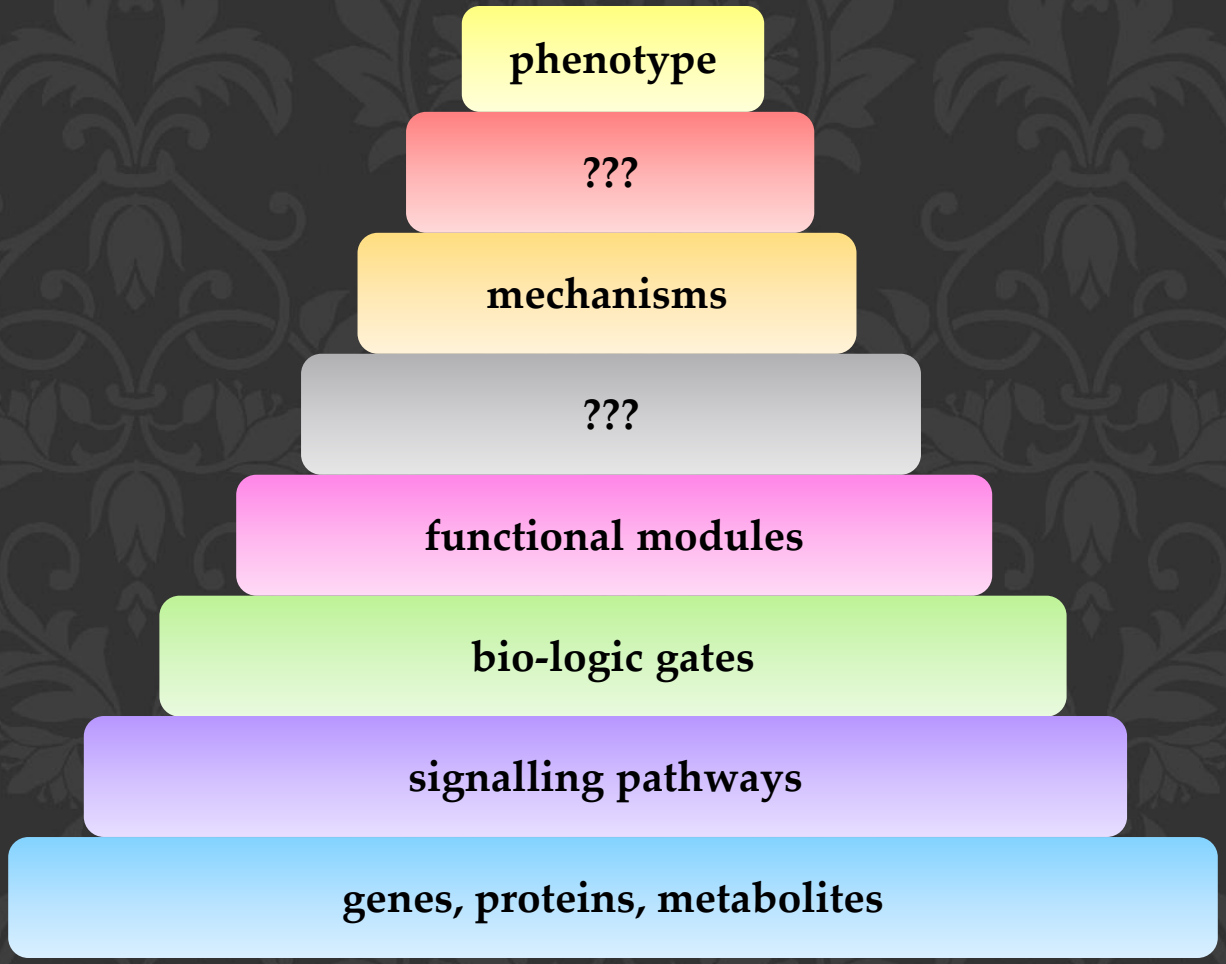
Challenges

Tower of abstractions in biology

Tower of abstractions in hardware

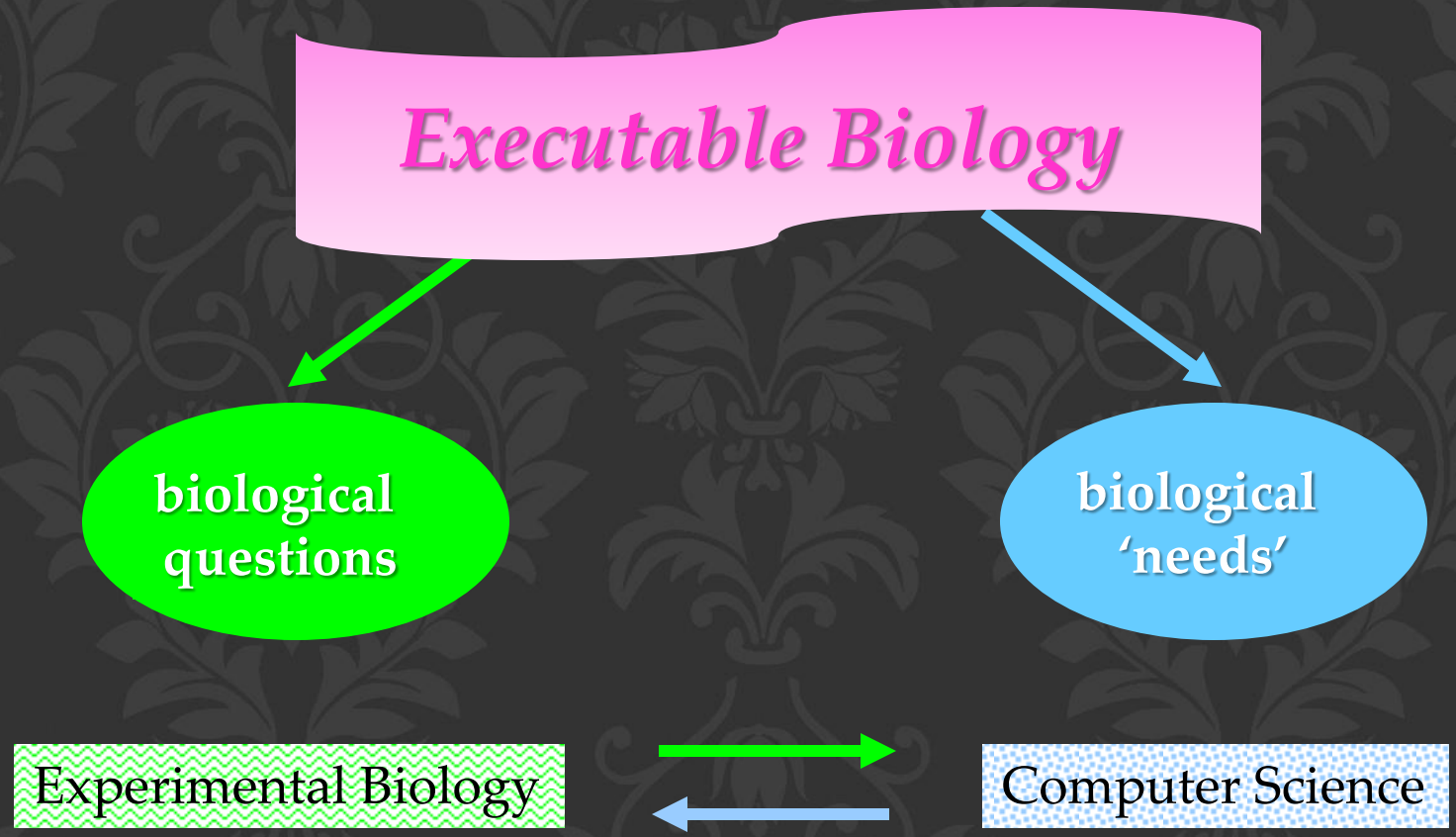


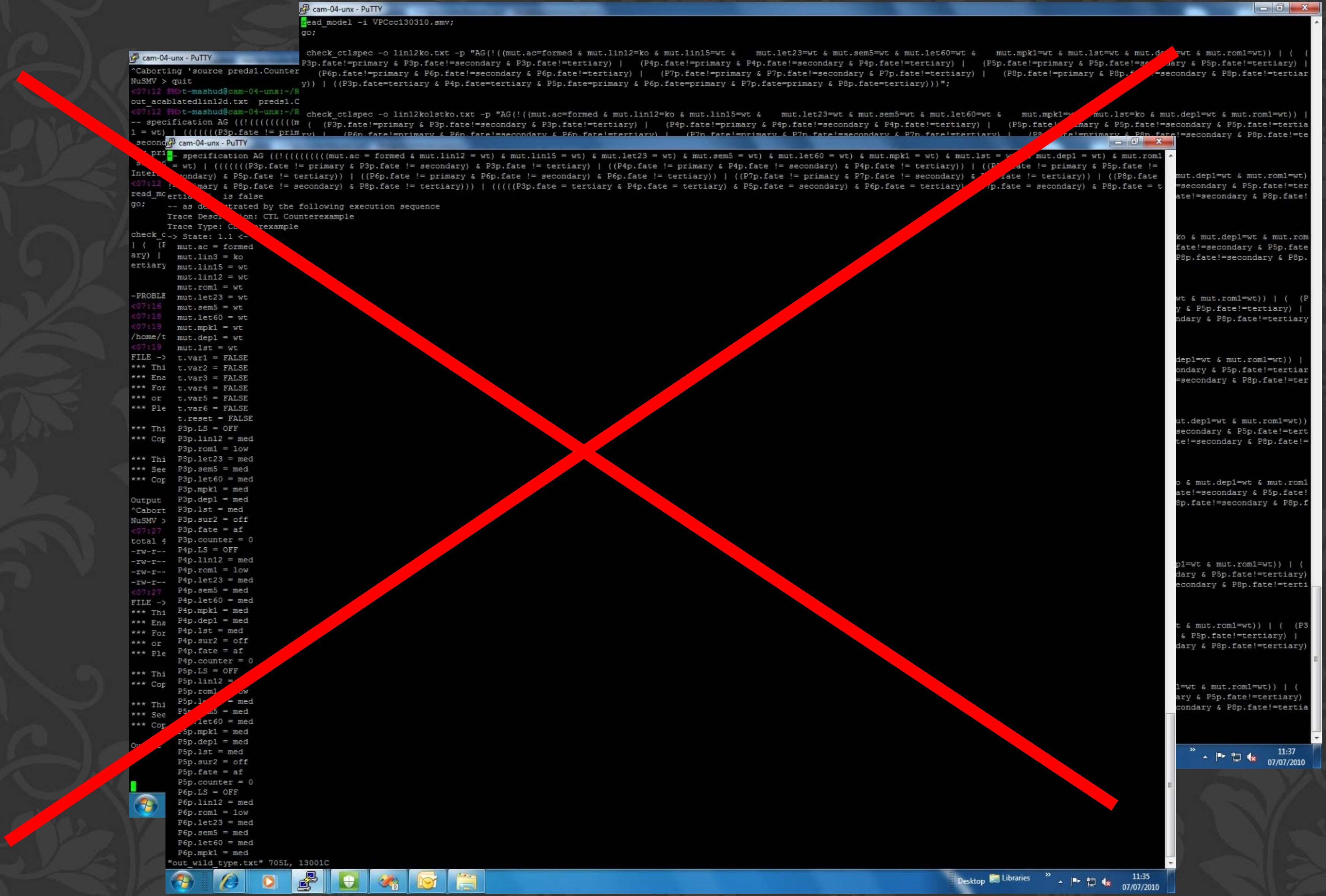
Tower of abstractions in biology



Fisher, Piterman & Vardi, FM 2011

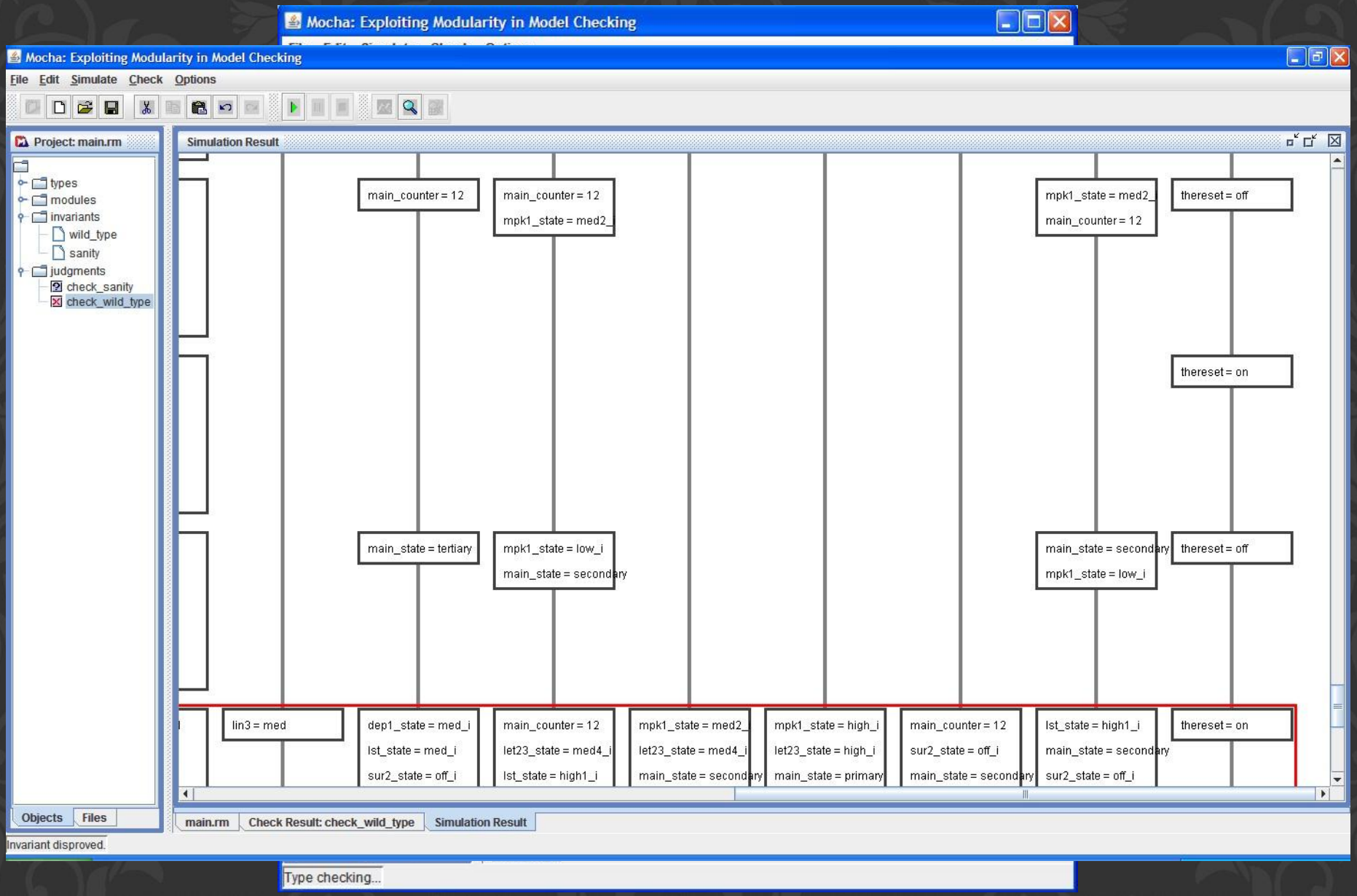
User-friendly modelling

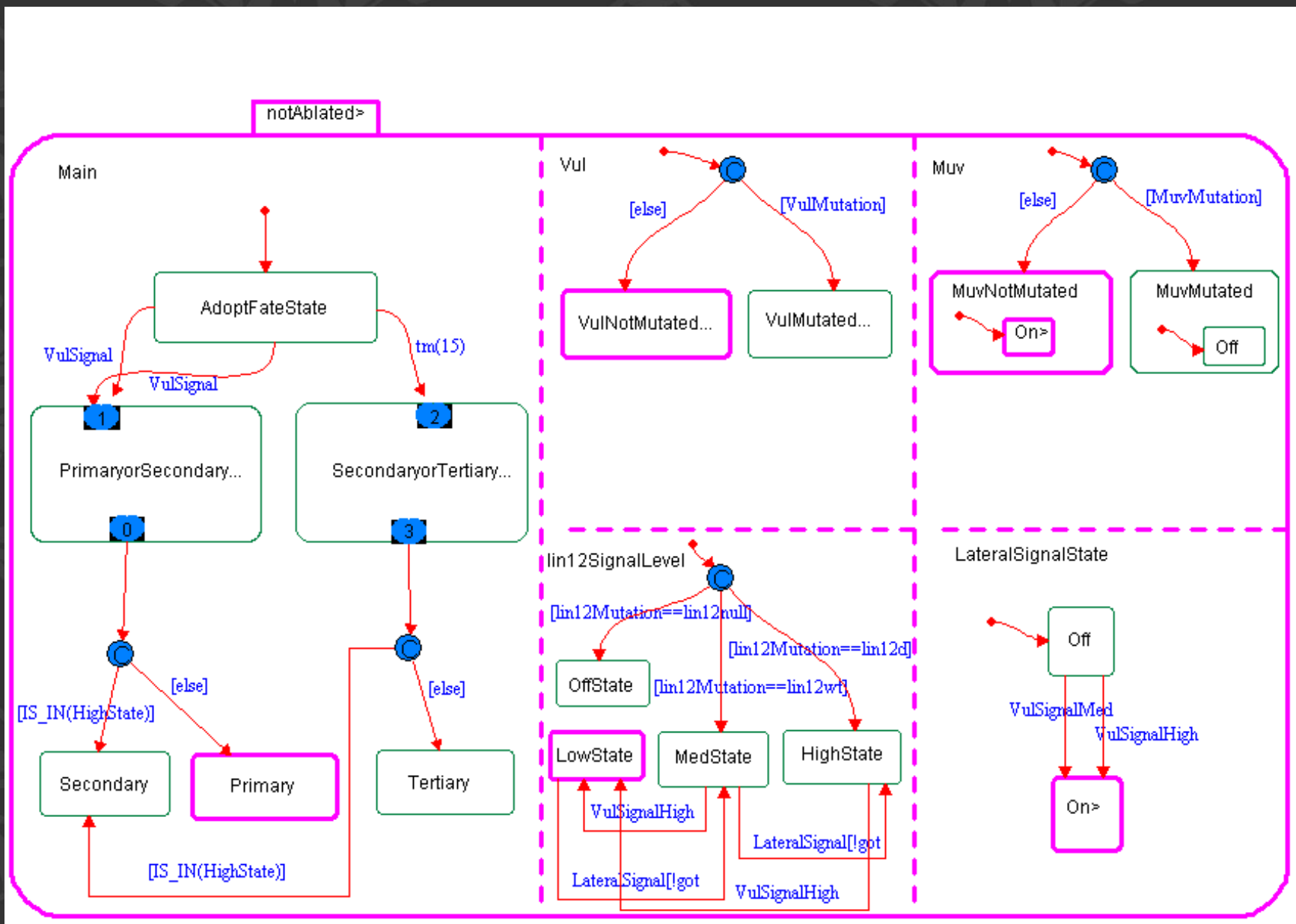

Executable Biology
biological questions
biological 'needs'
Experimental Biology
Computer Science



cam-04-unx - PuTTY
read_model -i VPCcc130310.smv;
go;
-- specification AG ((!((((((((((mut.ac = formed & mut.lin12 = wt) & mut.lin15 = wt) & mut.let23 = wt) & mut.sem5 = wt) & mut.let60 = wt) & mut.mpk1 = wt) & mut.lst =
is false
-- as demonstrated by the following execution sequence
Trace Description: CTL Counterexample
Trace Type: Counterexample
-> State: 1.1 <-
mut.ac = formed
mut.lin3 = ko
mut.lin15 = wt
mut.lin12 = wt
mut.rom1 = wt
mut.let23 = wt
mut.sem5 = wt
mut.let60 = wt
mut.mpk1 = wt
mut.dep1 = wt
mut.lst = wt
t.var1 = FALSE
t.var2 = FALSE
t.var3 = FALSE
t.var4 = FALSE
t.var5 = FALSE
t.var6 = FALSE
t.reset = FALSE
P3p.LS = OFF
P3p.lin12 = med
P3p.rom1 = low
P3p.let23 = med
P3p.sem5 = med
P3p.let60 = med
P3p.mpk1 = med
P3p.dep1 = med
P3p.lst = med
P3p.sur2 = off
P3p.fate = af
P3p.counter = 0
P4p.LS = OFF
P4p.lin12 = med
P4p.rom1 = low
P4p.let23 = med
P4p.sem5 = med
P4p.let60 = med
P4p.mpk1 = med
P4p.dep1 = med
P4p.lst = med
P4p.sur2 = off
P4p.fate = af
P4p.counter = 0
P5p.LS = OFF
P5p.let60 = med
P5p.mpk1 = med
P5p.dep1 = med
P5p.lst = med
P5p.sur2 = off
P5p.fate = af
P5p.counter = 0
P6p.LS = OFF
P6p.lin12 = med
P6p.rom1 = low
P6p.let23 = med
P6p.sem5 = med
P6p.let60 = med
P6p.mpk1 = med
"out_wild_type.txt" 705L, 13001C
11:35
07/07/2010
11:37
07/07/2010

Not talking about GUI...




notAblated>
Main
AdoptFateState
VulSignal
VulSignal
tm(15)
1
2
PrimaryorSecondary...
SecondaryorTertiary...
0
3
[else]
[IS_IN(HighState)]
[else]
Secondary
Primary
Tertiary
[IS_IN(HighState)]
Vul
[else]
[VulMutation]
VulNotMutated...
VulMutated...
Muv
[else]
[MuvMutation]
MuvNotMutated
On>
MuvMutated
Off
lin12SignalLevel
[lin12Mutation==lin12null]
[lin12Mutation==lin12d]
[lin12Mutation==lin12wt]
OffState
LowState
MedState
HighState
VulSignalHigh
LateralSignal[!got
LateralSignal[!got
VulSignalHigh
LateralSignalState
Off
VulSignalMed
VulSignalHigh
On>

Bio Model Analyzer

Proving Stabilization of Biological Systems

Byron Cook
MSRC

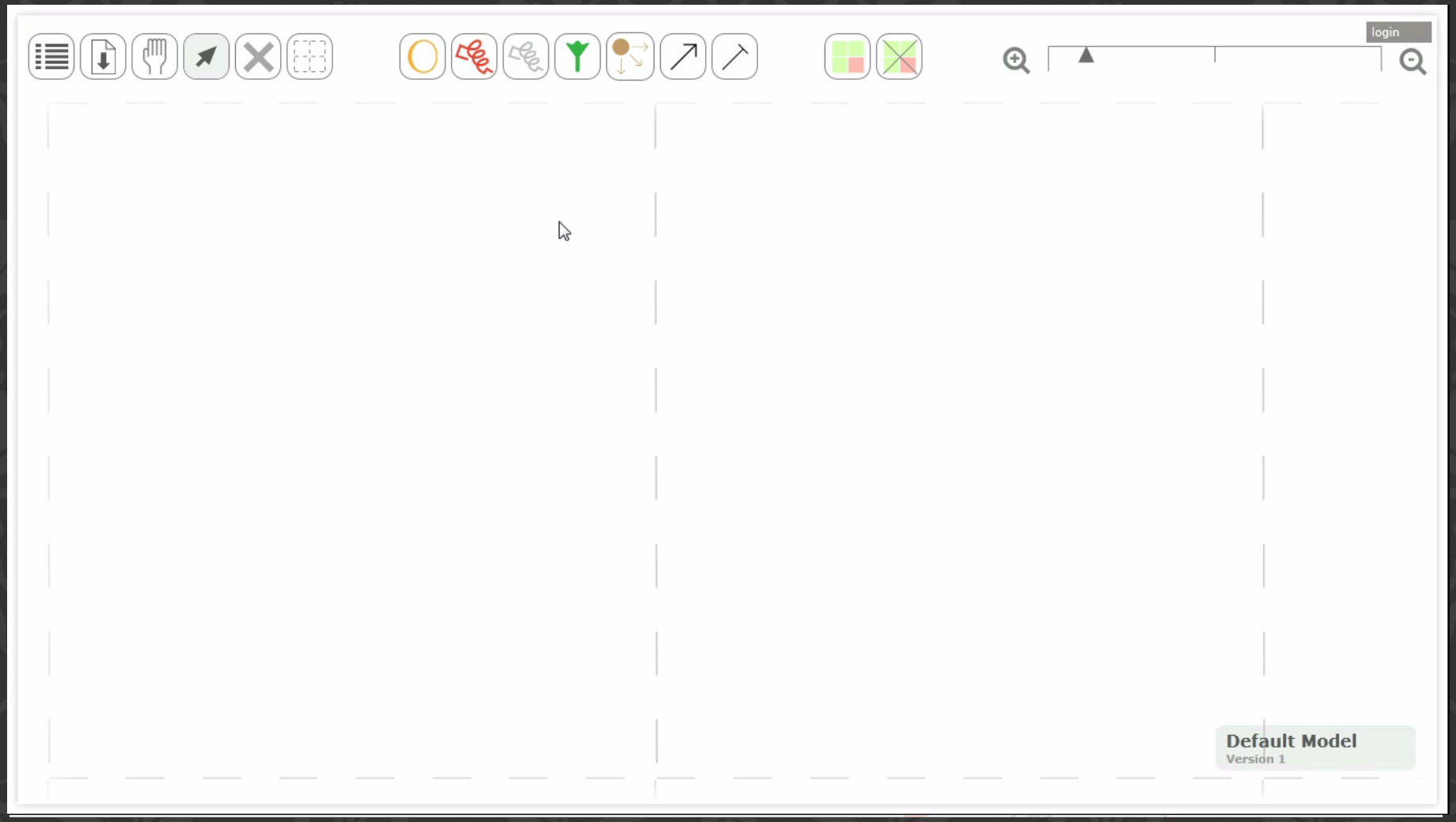
Alex Taylor
MSRC

Samin Ishtiaq
MSRC

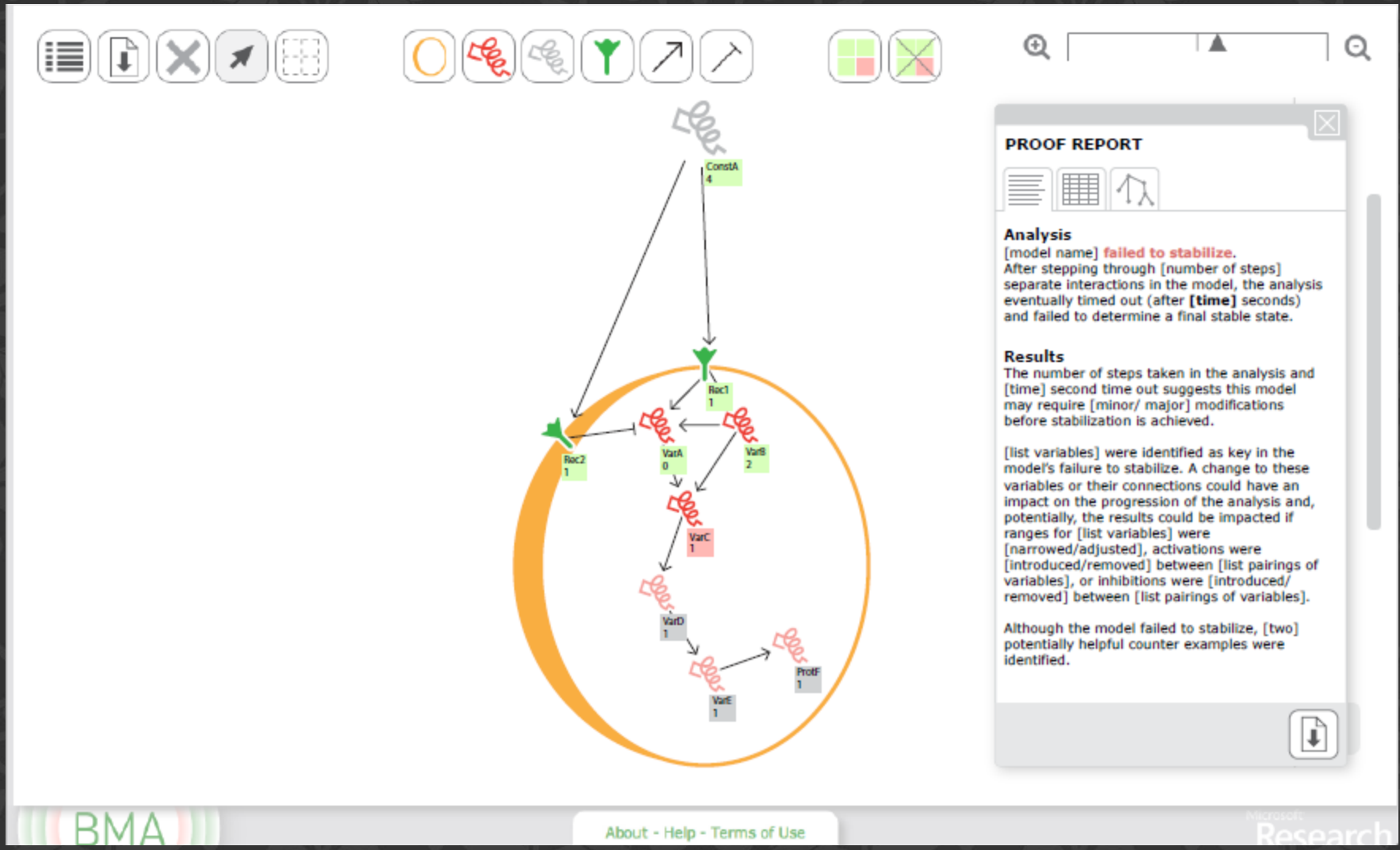
Nir Piterman
Univ. of Leicester

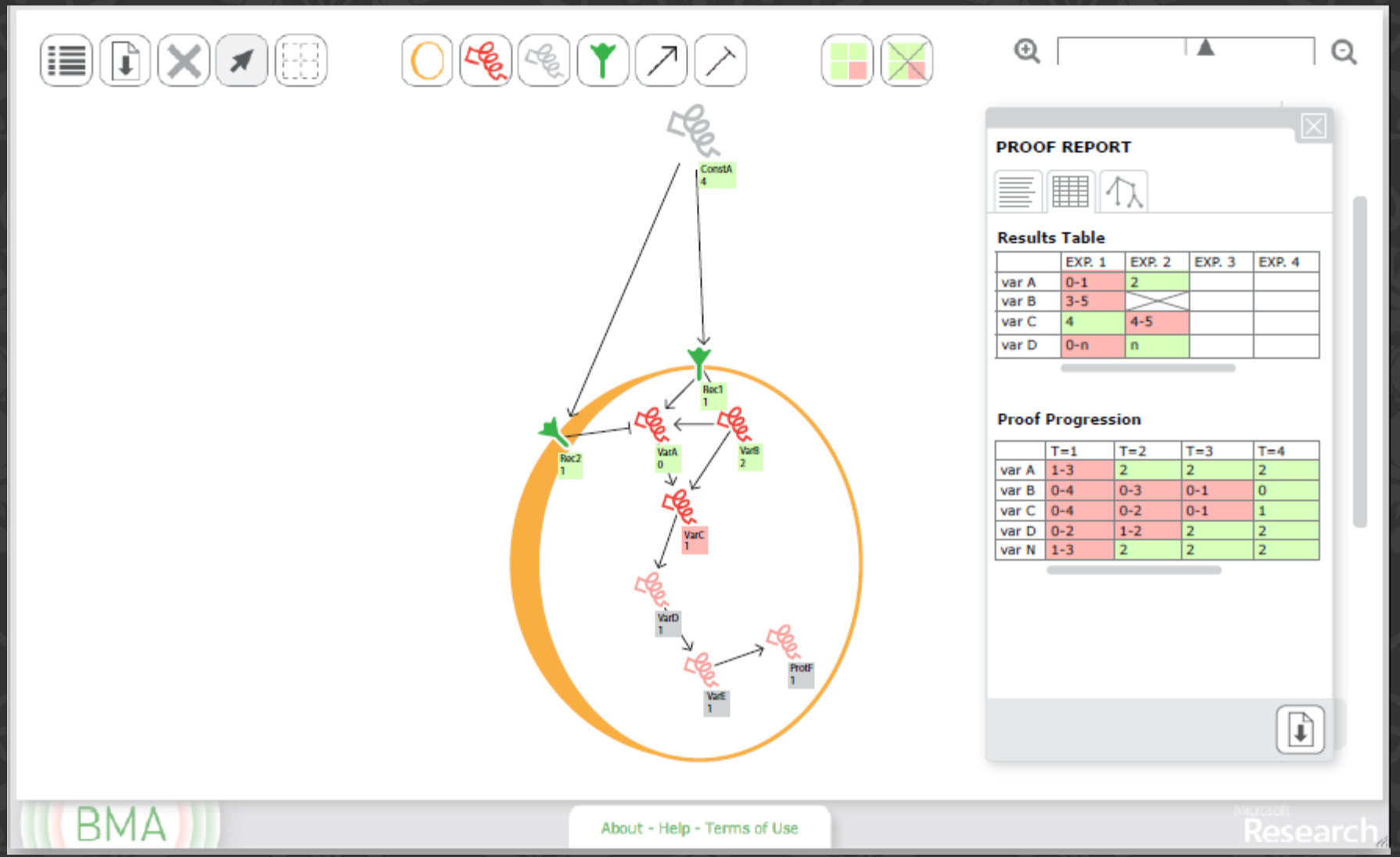
***VMCAI* 2011, *CAV* 2012**

http://biomodelanalyzer.research.microsoft.com/



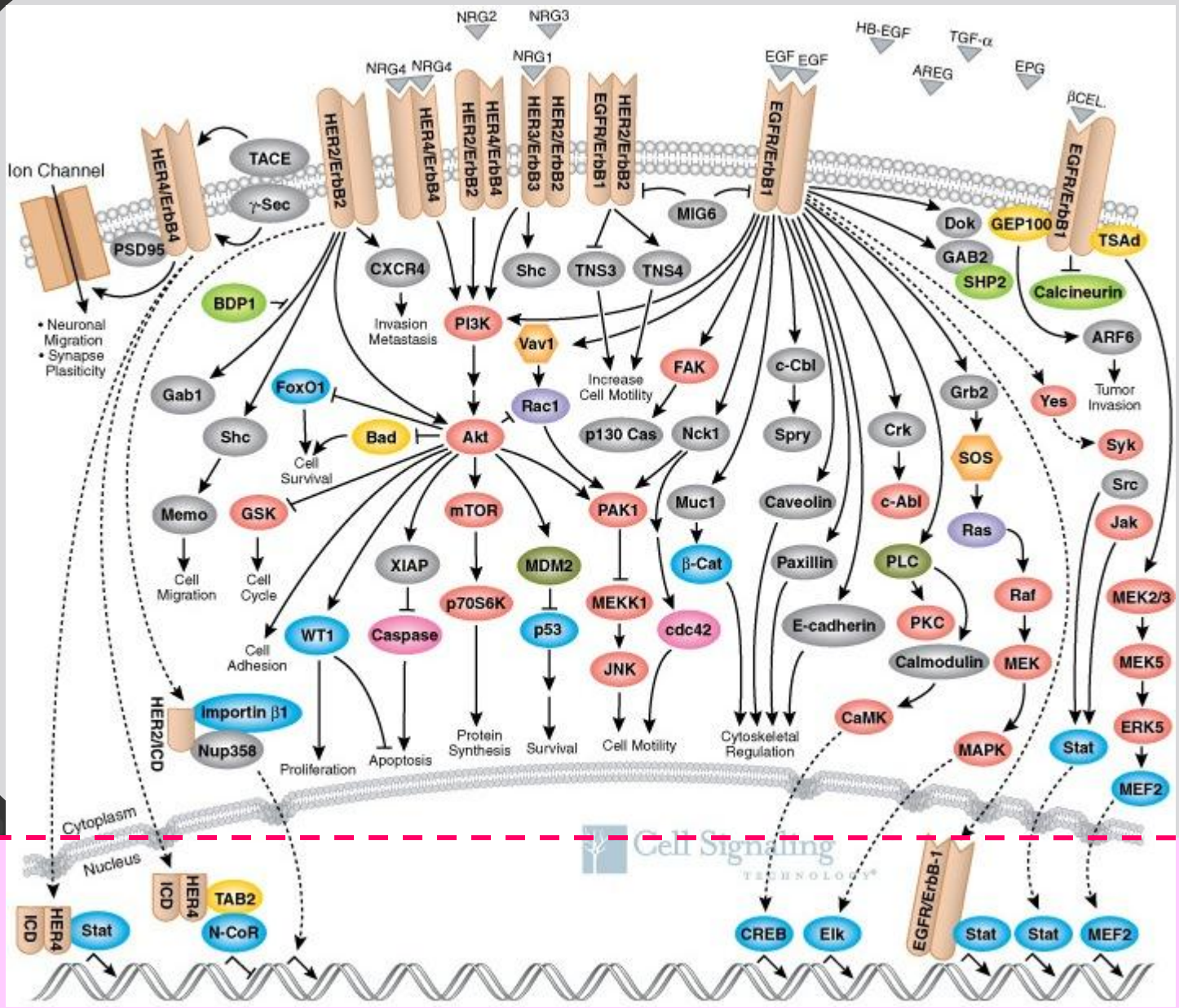
Proof visualization




ConstA
4
Rec1
1
Rec2
1
VarA
0
VarB
2
VarC
1
VarD
1
VarE
1
ProtF
1
PROOF REPORT
Results Table
EXP. 1
EXP. 2
EXP. 3
EXP. 4
var A
0-1
2
var B
3-5
var C
4
4-5
var D
0-n
n
Proof Progression
T=1
T=2
T=3
T=4
var A
1-3
2
2
2
var B
0-4
0-3
0-1
0
var C
0-4
0-2
0-1
1
var D
0-2
1-2
2
2
var N
1-3
2
2
2
BMA
About - Help - Terms of Use
Microsoft Research

Multi-scale modelling

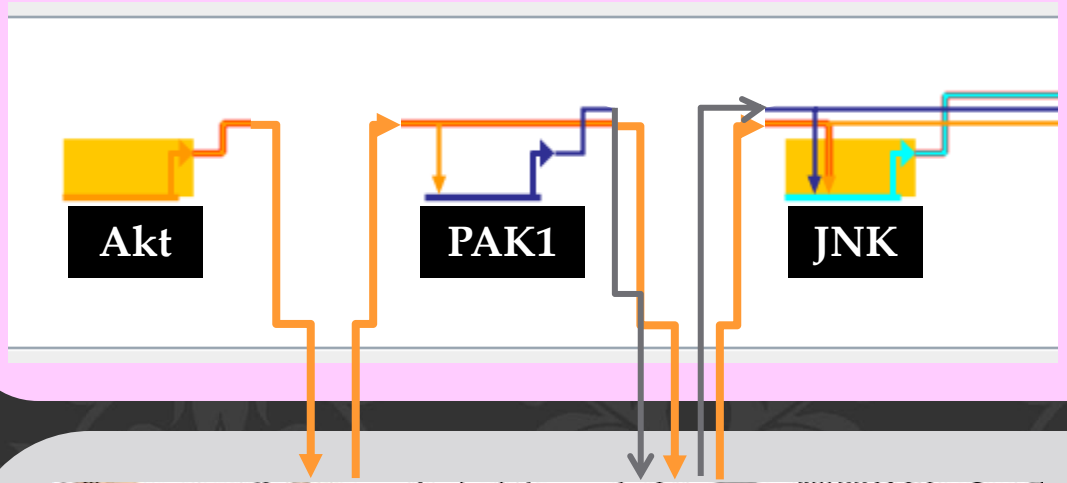
Different time scales and space



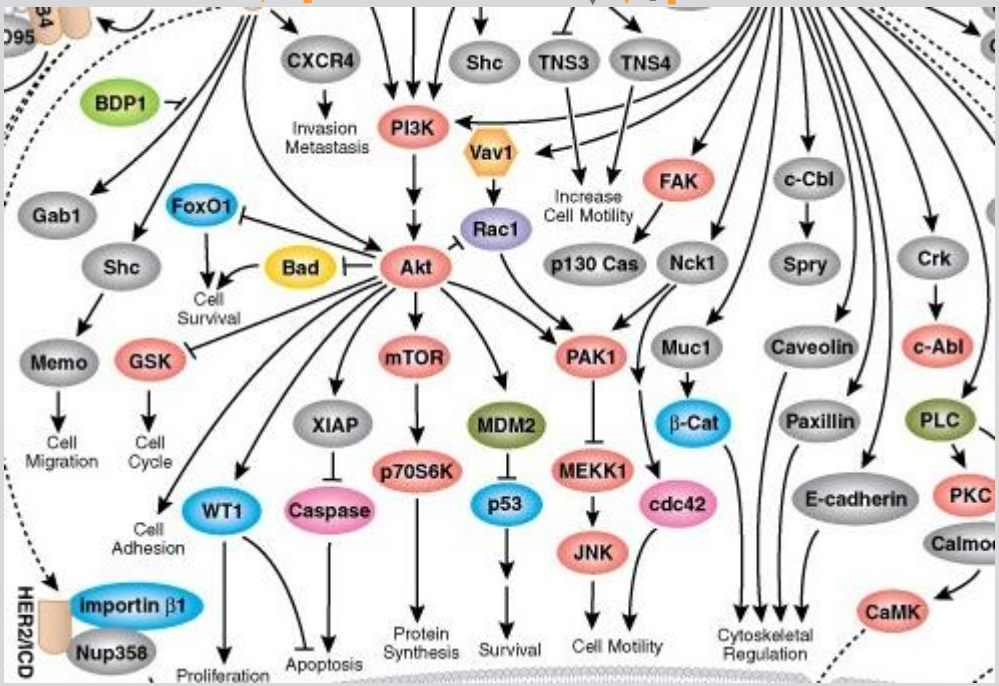
Cell Signalling

Gene Regulation

Feedback between the levels

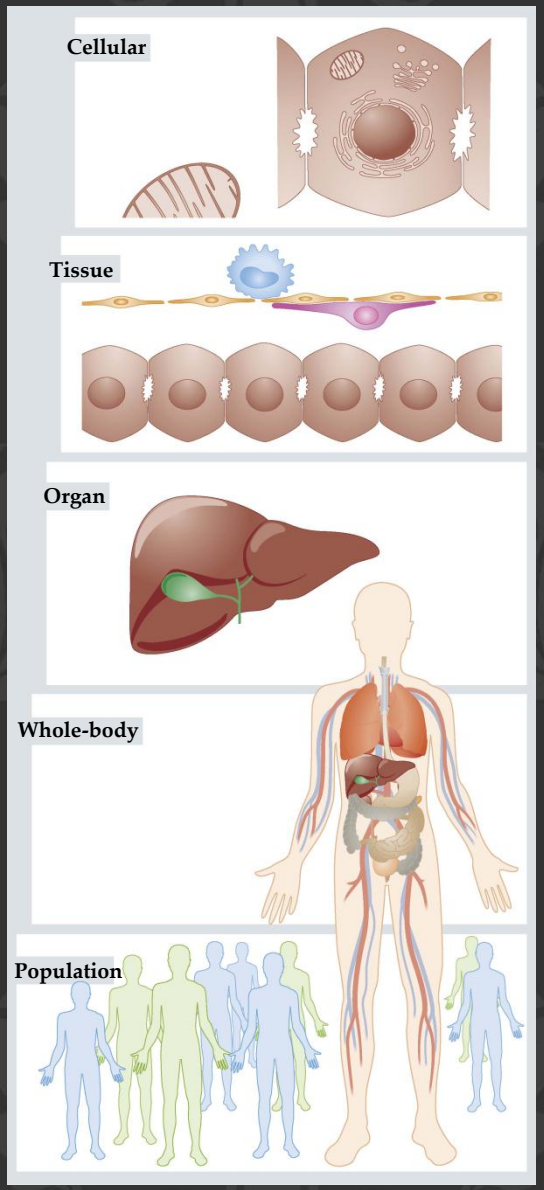


Gene Regulation



Cell Signalling

A multi-scale presentation of human physiology



Lars Kuepfer *Molecular Systems Biology* 2010

Thanks!...