Parallel Composition in Biology

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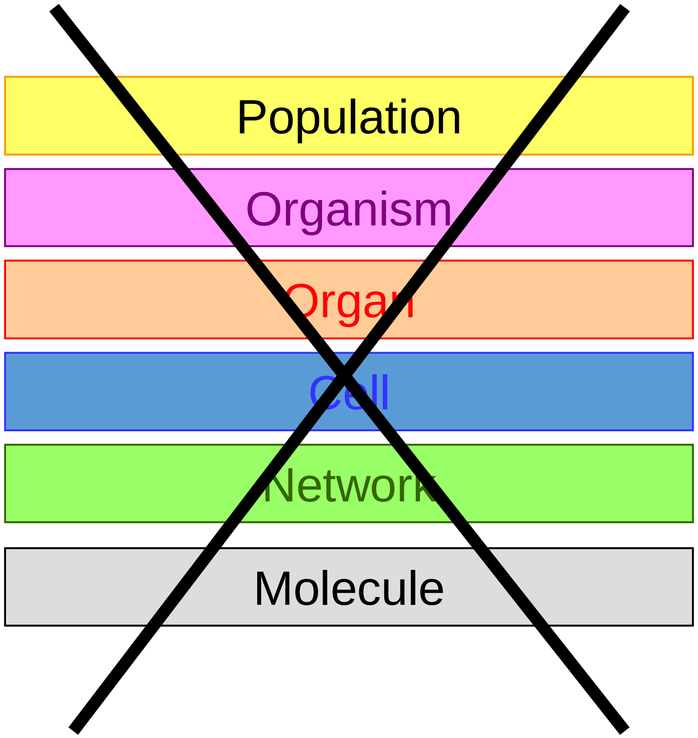
Based on joint work with:

J. Fisher, A. Hajnal, B. Hall, T. A. Henzinger, M. Mateescu, D. Nickovic, A.V. Singh, and M.Y. Vardi

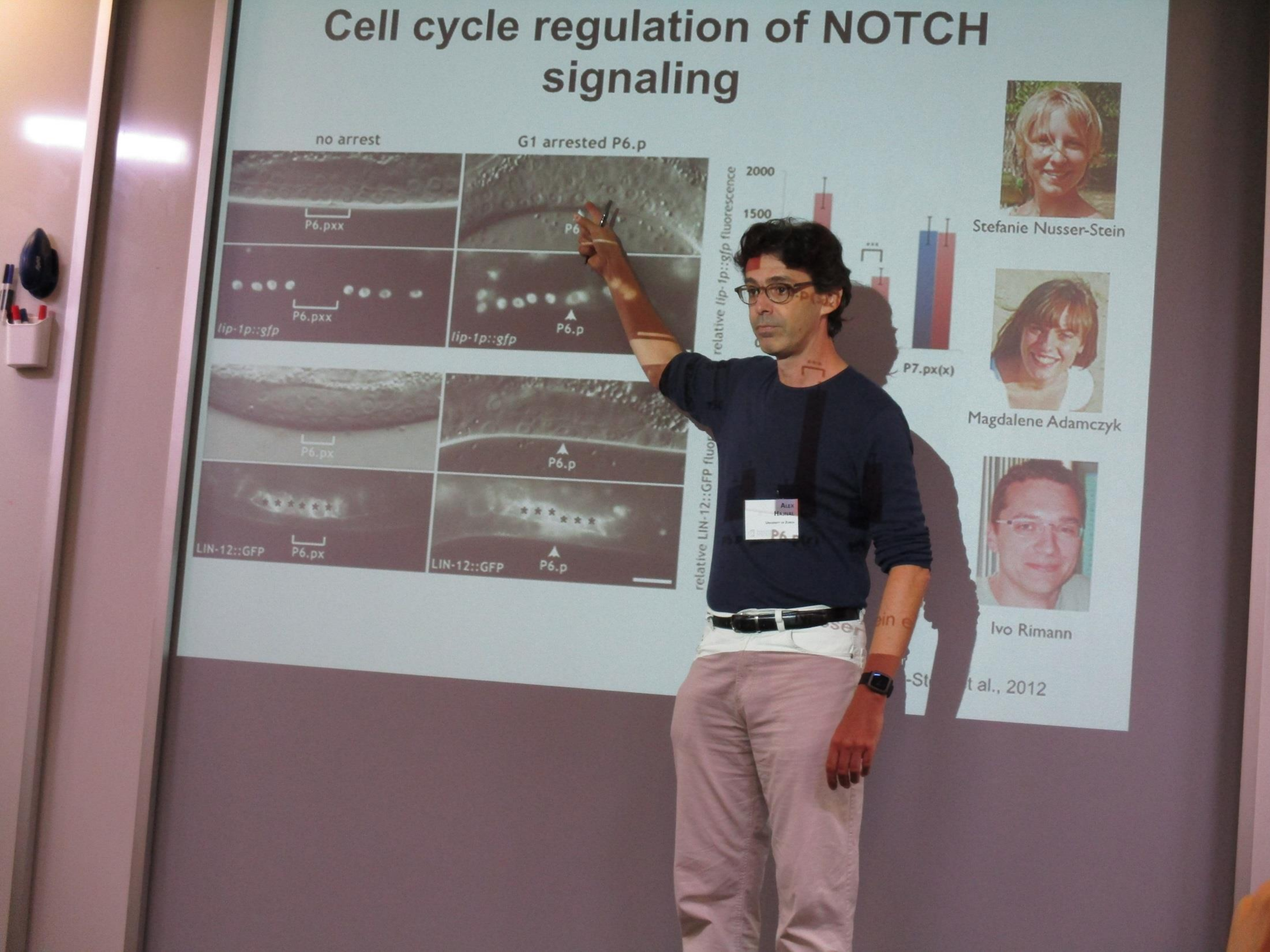
Are there useful macros to structure the "hairball"?

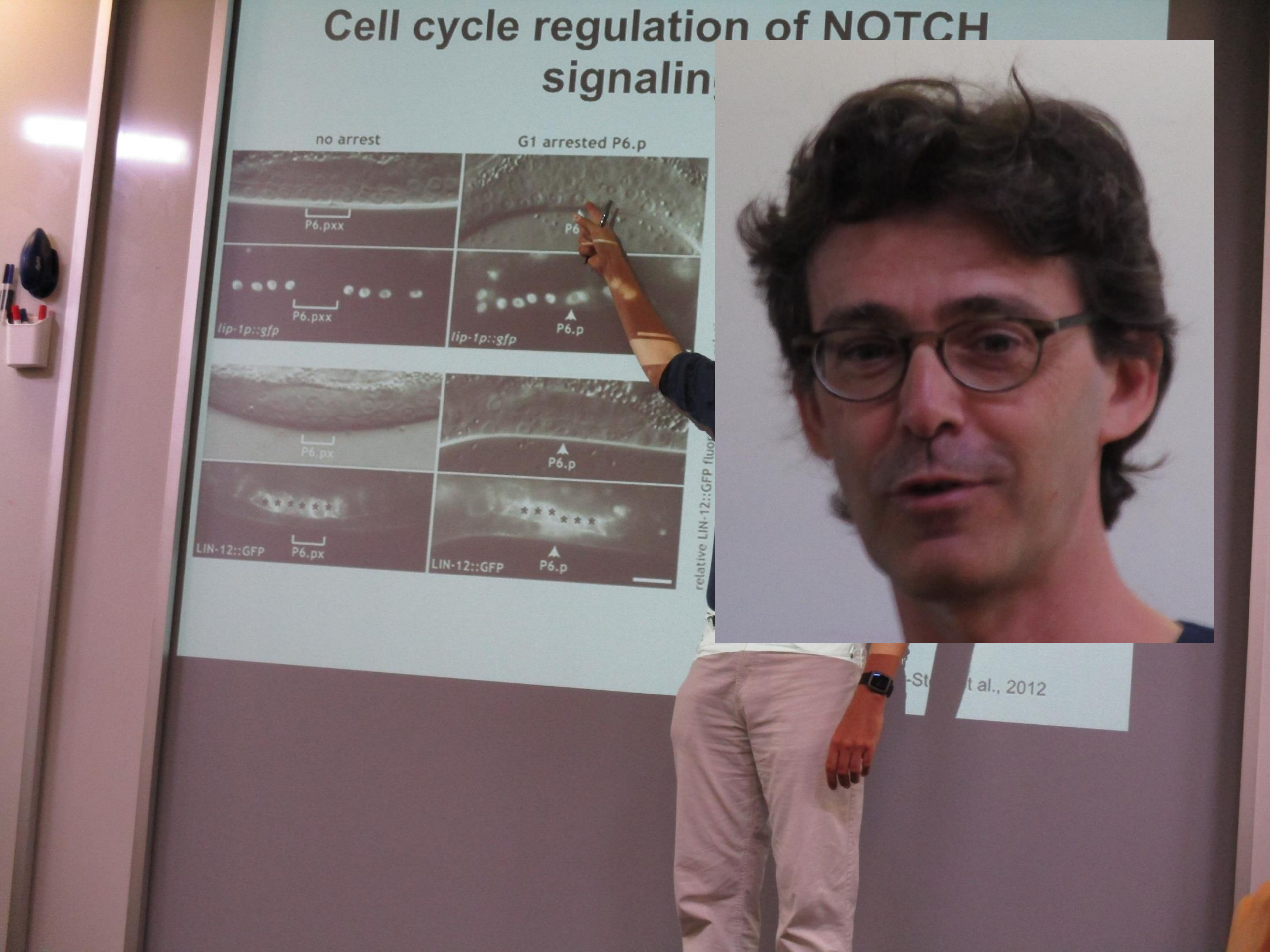


We are looking for the organizing principle:
the programming language,
only then for the program!

Settling on less ambitious goals (for now):

- Create useful models of certain biological phenomena.
- Understand the principles that allow to create certain types of models.
  - Create models.
- Improve analysis for these kinds of models.
  - Verify them.
- Improve tool support for these kinds of models.


Cell cycle regulation of NOTCH signaling
no arrest
G1 arrested P6.p
P6.pxx
lip-1p::gfp
P6.p
P6.px
LIN-12::GFP
2000
1500
relative lip-1p::gfp fluorescence
P7.px(x)
Stefanie Nusser-Stein
Magdalene Adamczyk
Ivo Rimann
al., 2012


Cell cycle regulation of NOTCH
no arrest
G1 arrested P6.p
P6.pxx
lip-1p::gfp
P6.pxx
lip-1p::gfp
P6.p
P6.px
P6.p
LIN-12::GFP
P6.px
LIN-12::GFP
P6.p

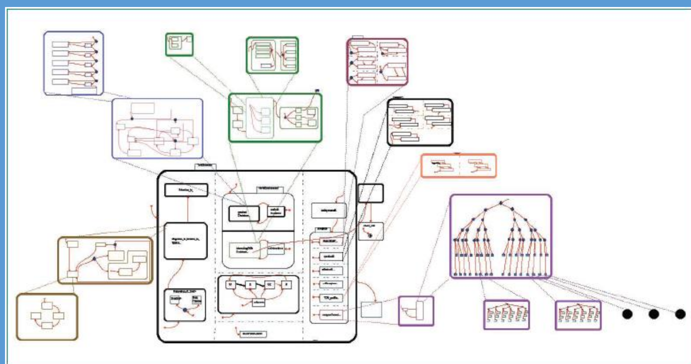
Assumptions

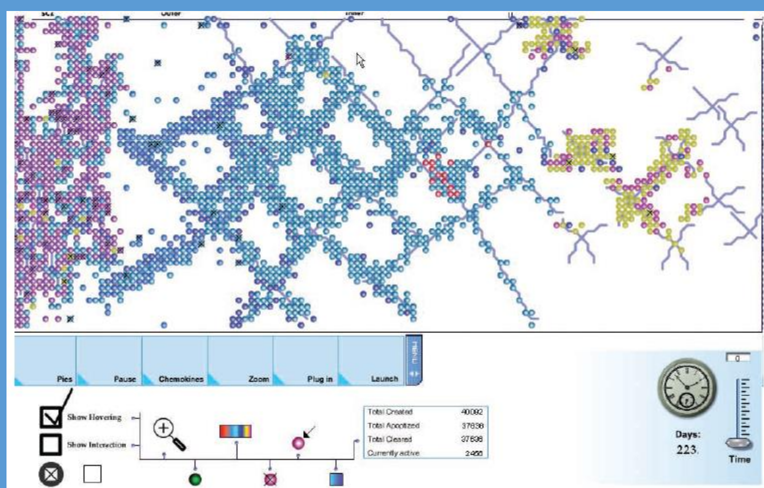
- Models are **very** abstract:
  - Personal belief.
  - Personal preference.
- We **want** to use a simple state machine to represent a biological process (usually at a cell level).
- We **want** to represent the process in several cells.
- We **want** them to run concurrently.
- We **want** simulation and additional analysis.

Examples

Efroni, Cohen, and Harel

Computer **38**:1 (2005)



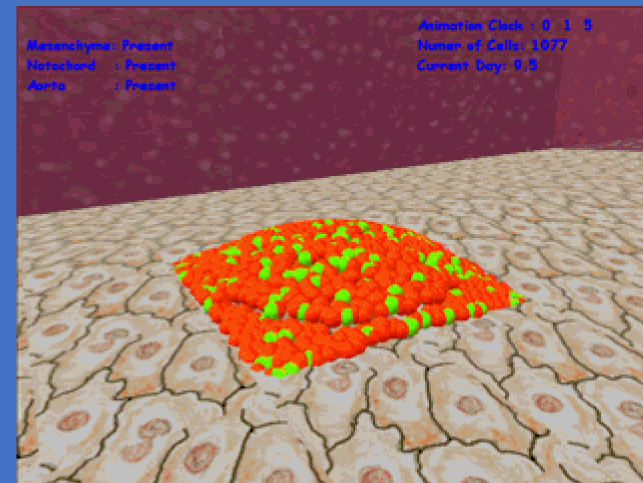


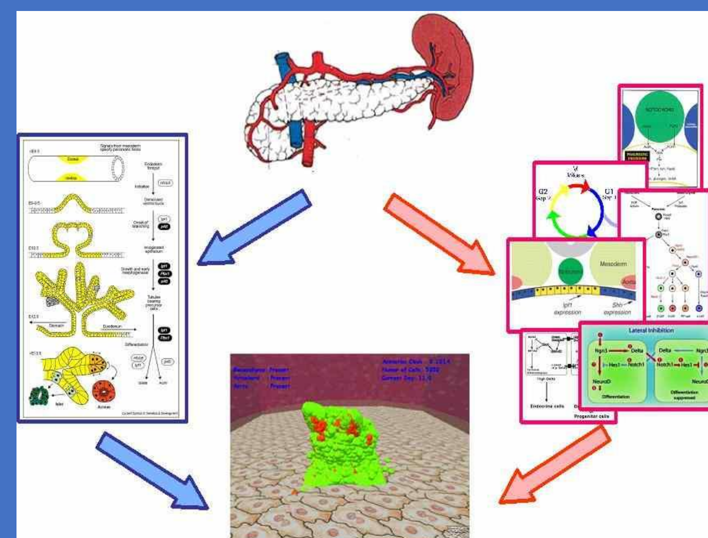
PLOS Computational Biology **3**:1 (2007)

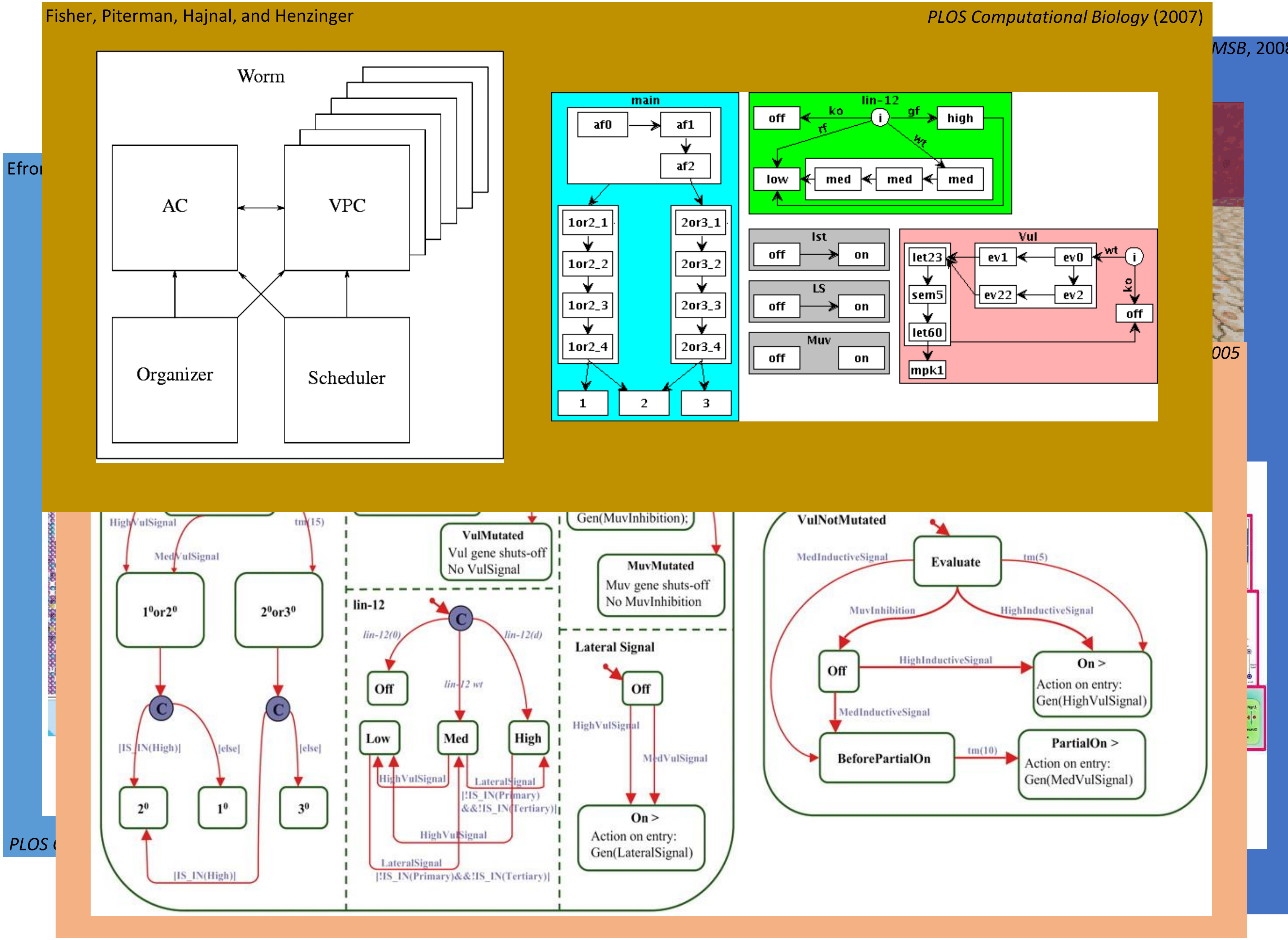
Genome Research **13** (2003)

Setty and Harel

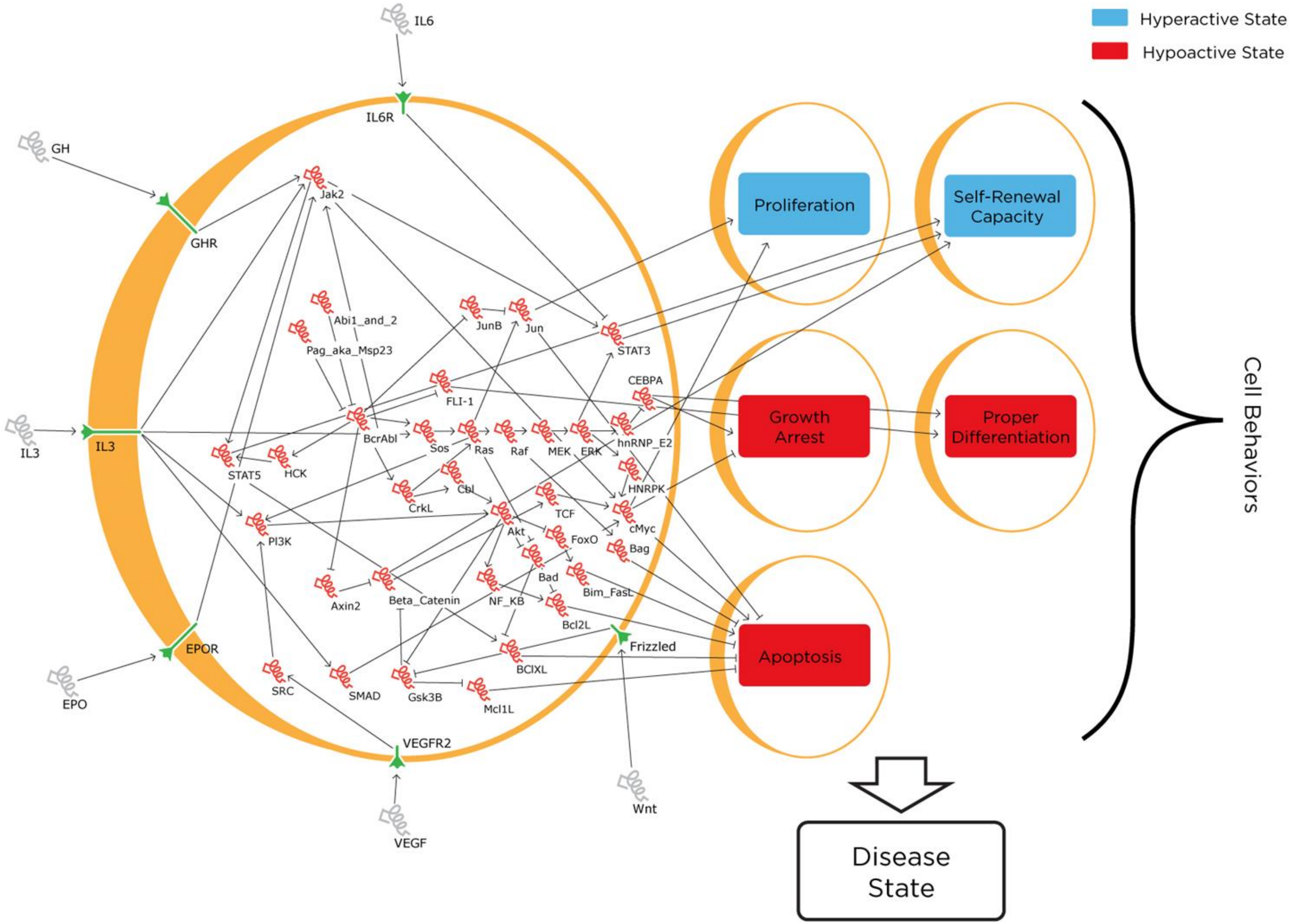
FMSB, 2008

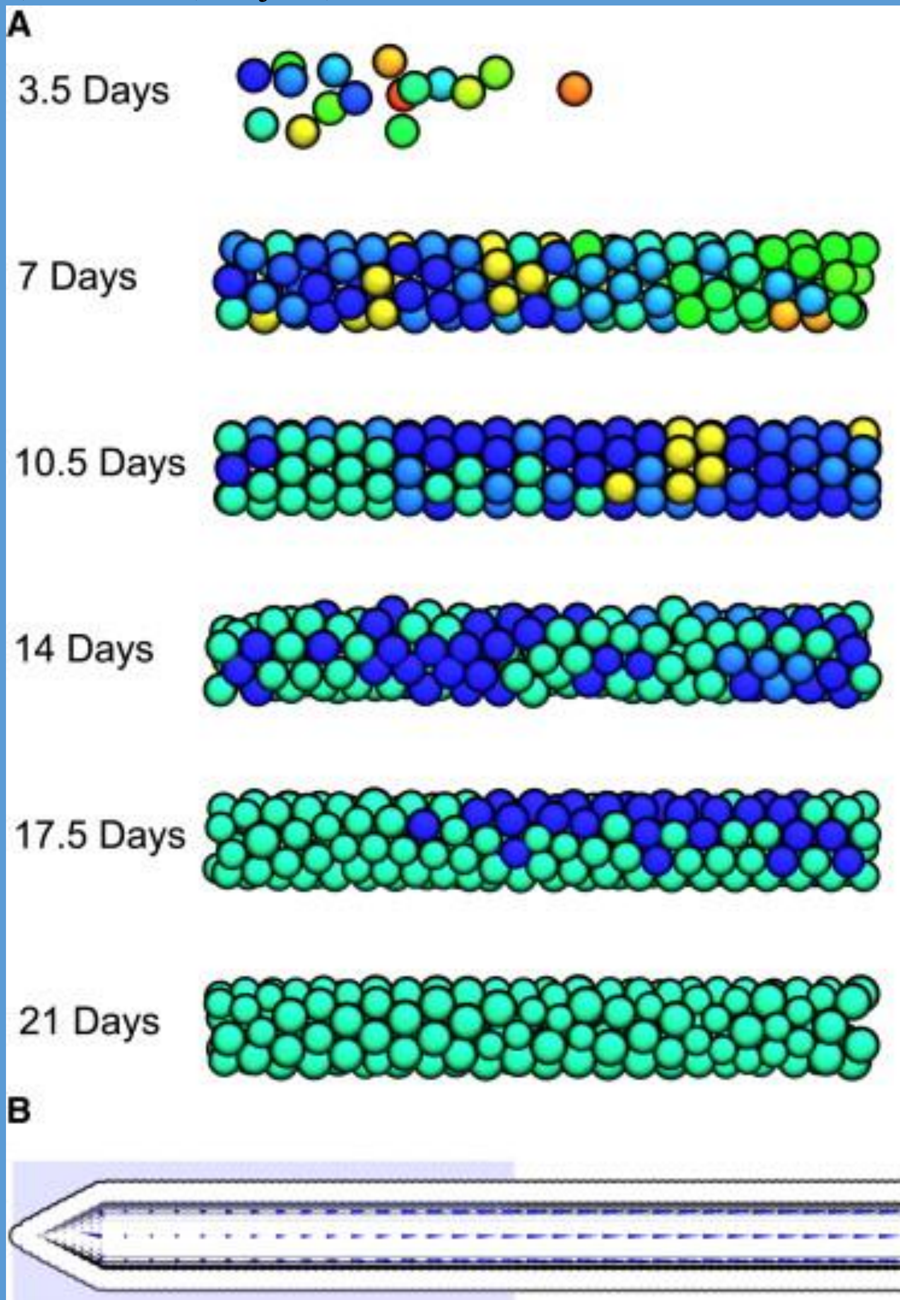


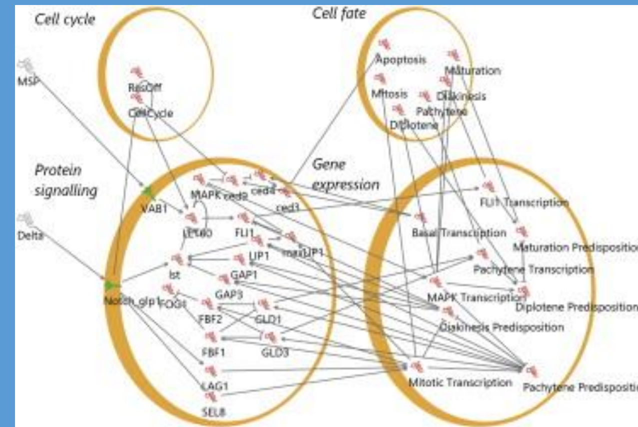


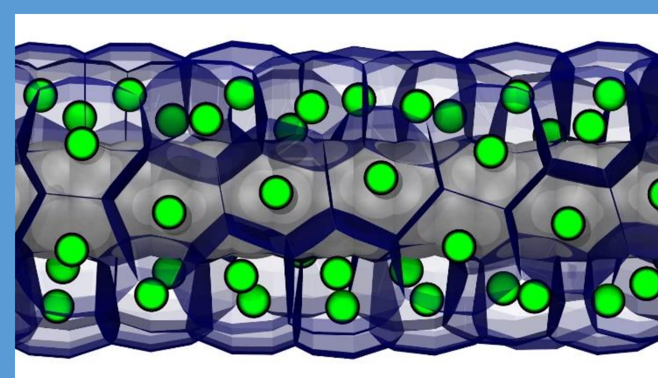


Fisher, Piterman, Hajnal, and Henzinger
PLOS Computational Biology (2007)
MSB, 2008
Efro
005
PLOS
Worm
AC
VPC
Organizer
Scheduler
main
af0
af1
af2
1or2_1
1or2_2
1or2_3
1or2_4
2or3_1
2or3_2
2or3_3
2or3_4
1
2
3
lin-12
off
ko
i
gf
high
rf
wt
low
med
med
med
lst
off
on
LS
off
on
Muv
off
on
Vul
let23
sem5
let60
mpk1
ev1
ev0
ev22
ev2
wt
i
ko
off
HighVulSignal
tm(15)
MedVulSignal
1⁰or2⁰
2⁰or3⁰
C
C
[IS_IN(High)]
[else]
[else]
2⁰
1⁰
3⁰
[IS_IN(High)]
VulMutated
Vul gene shuts-off
No VulSignal
lin-12
C
lin-12(0)
lin-12(d)
lin-12 wt
Off
Low
Med
High
HighVulSignal
LateralSignal
[!IS_IN(Primary)
&&!IS_IN(Tertiary)]
HighVulSignal
LateralSignal
[!IS_IN(Primary)&&!IS_IN(Tertiary)]
Gen(MuvInhibition);
MuvMutated
Muv gene shuts-off
No MuvInhibition
Lateral Signal
Off
HighVulSignal
MedVulSignal
On >
Action on entry:
Gen(LateralSignal)
VulNotMutated
Evaluate
MedInductiveSignal
tm(5)
MuvInhibition
HighInductiveSignal
Off
HighInductiveSignal
On >
Action on entry:
Gen(HighVulSignal)
MedInductiveSignal
BeforePartialOn
tm(10)
PartialOn >
Action on entry:
Gen(MedVulSignal)


Hyperactive State
Hypoactive State
IL6
IL6R
GH
GHR
IL3
EPO
EPOR
VEGF
VEGFR2
Wnt
Frizzled
Jak2
Abi1_and_2
Pag_aka_Msp23
JunB
Jun
STAT3
FLI-1
CEBPA
BcrAbl
Sos
Ras
Raf
MEK
ERK
hnRNP_E2
STAT5
HCK
Cbl
CrkL
TCF
HNRPK
PI3K
Akt
FoxO
cMyc
Bag
Bad
Bim_FasL
Axin2
Beta_Catenin
NF_KB
Bcl2L
SRC
SMAD
Gsk3B
BCIXL
Mcl1L
Proliferation
Self-Renewal Capacity
Growth Arrest
Proper Differentiation
Apoptosis
Cell Behaviors
Disease State

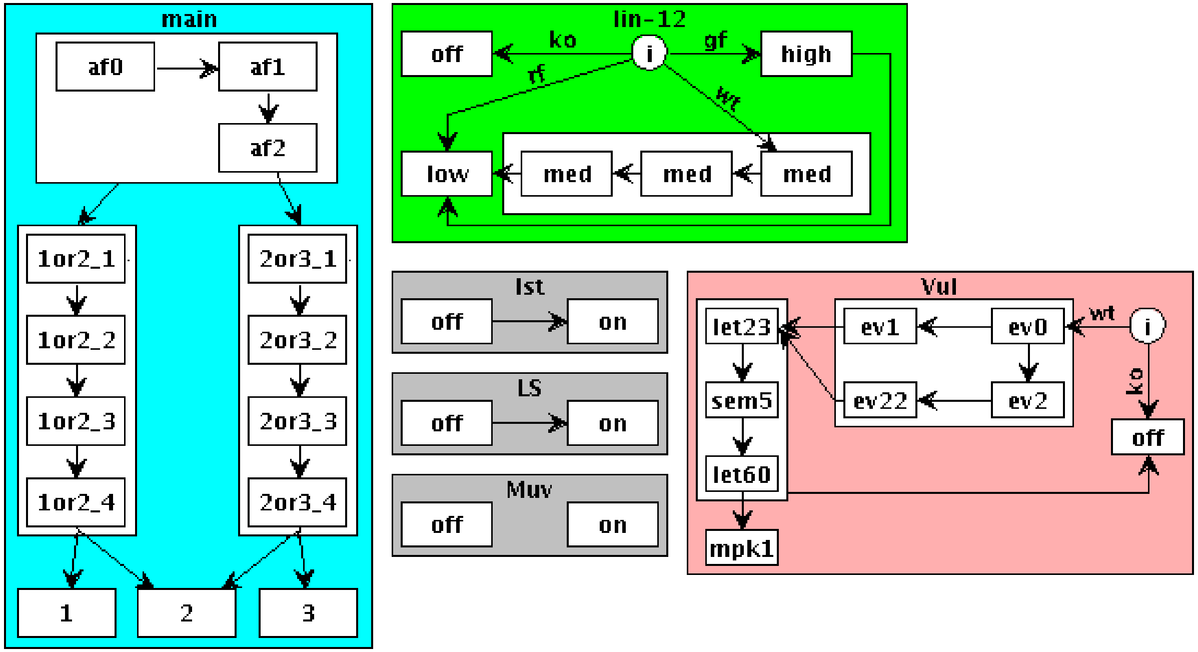

A
3.5 Days
7 Days
10.5 Days
14 Days
17.5 Days
21 Days
B

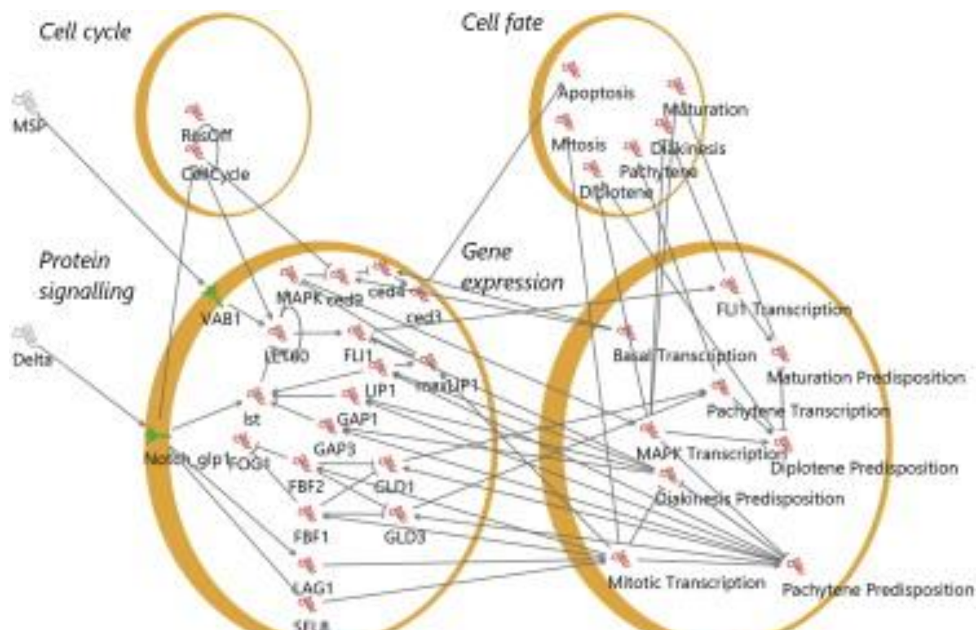

Cell cycle
Cell fate
Protein signalling
Gene expression
MSP
Delta
Apoptosis
Maturation
Mitosis
Diakinesis
Pachytene
Diplotene
VAB1
FLI1 Transcription
Basal Transcription
Maturation Predisposition
Pachytene Transcription
MAPK Transcription
Diplotene Predisposition
Diakinesis Predisposition
Mitotic Transcription
Pachytene Predisposition
GAP1
GAP3
FBF2
FBF1
GLD1
GLD3
LAG1
SEL8



What's a cell?

- Each cell is a state machine.
- They take discrete transitions:
  - Can depend on outside information (location/neighbours/environment).
  - Can be deterministic/nondeterministic/stochastic.
- The model consists of coordinating these changes across many cells.


main
af0
af1
af2
1or2_1
1or2_2
1or2_3
1or2_4
2or3_1
2or3_2
2or3_3
2or3_4
1
2
3
lin-12
off
ko
i
gf
high
rf
wt
low
med
med
med
lst
off
on
LS
off
on
Muv
off
on
Vul
let23
ev1
ev0
wt
i
sem5
ev22
ev2
ko
off
let60
mpk1

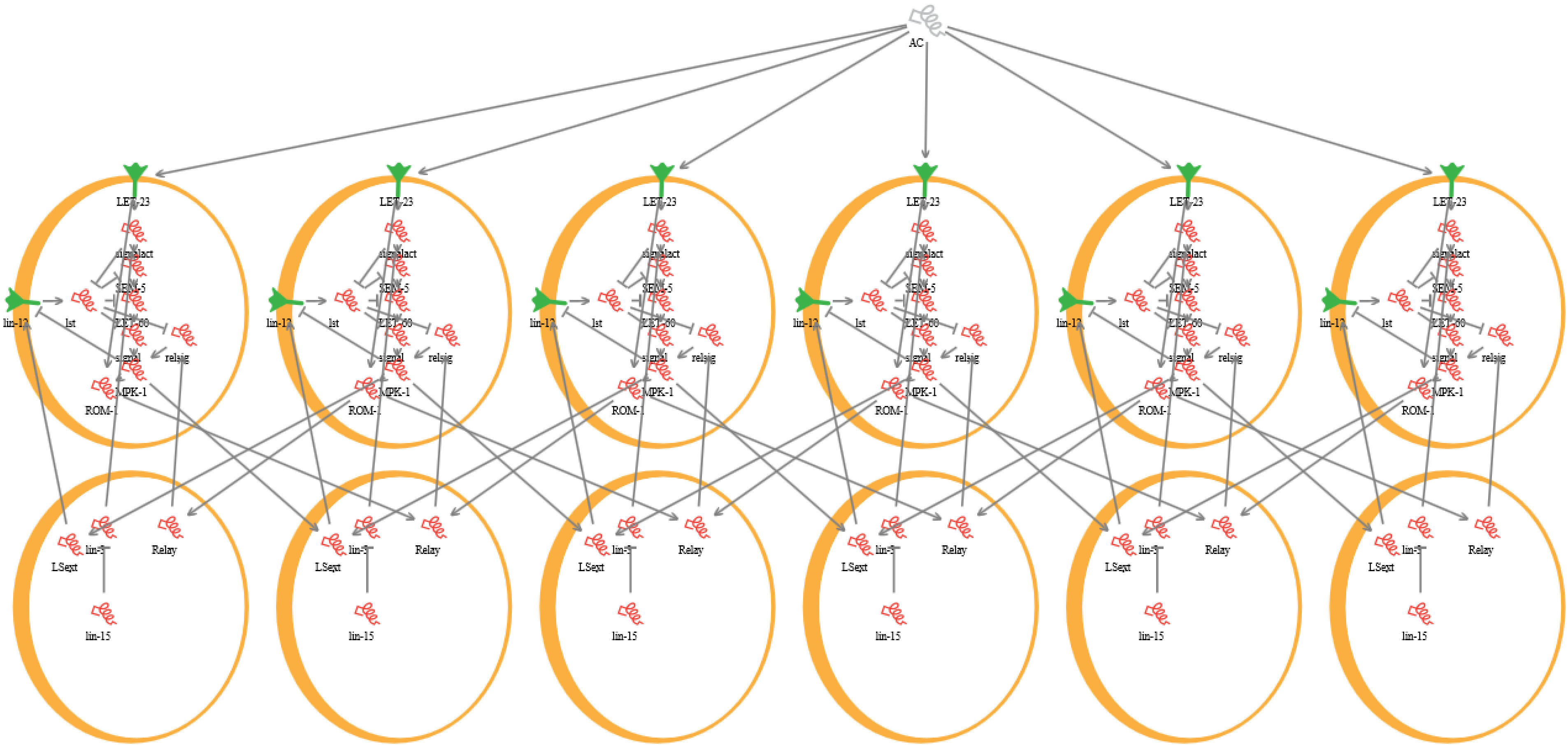

Cell cycle
Cell fate
MSP
RasOff
CellCycle
Apoptosis
Maturation
Mitosis
Diakinesis
Pachytene
Diplotene
Protein signalling
Gene expression
VAB1
MAPK
ced3
ced4
FLI1 Transcription
Delta
LET60
FLI1
Basal Transcription
Maturation Predisposition
UP1
lst
GAP1
Pachytene Transcription
MAPK Transcription
Notch_glp1
FOG1
GAP3
Diplotene Predisposition
FBF2
GLD1
Diakinesis Predisposition
FBF1
GLD3
LAG1
Mitotic Transcription
Pachytene Predisposition
SEL8

Parallel Composition

- Putting multiple cells together.
- When does each cell change its state compared to other cells?
- Classical answers:
  - All together: all cells read current values and change to new values.
  - One by one: choose a cell, it reads current values, and changes to new values.

From Synchrony to Timed

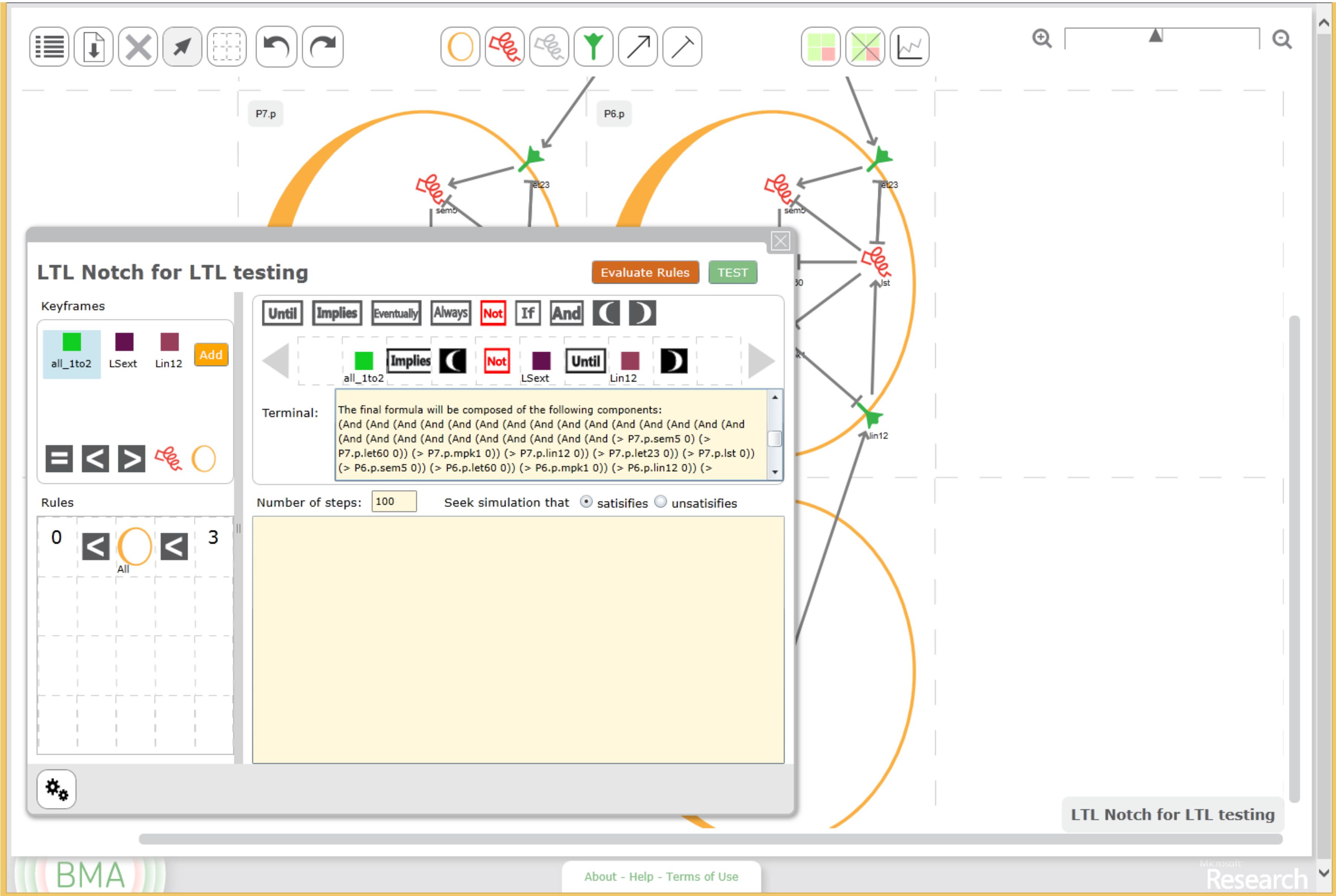
BioModelAnalyzer



Qualitative Networks

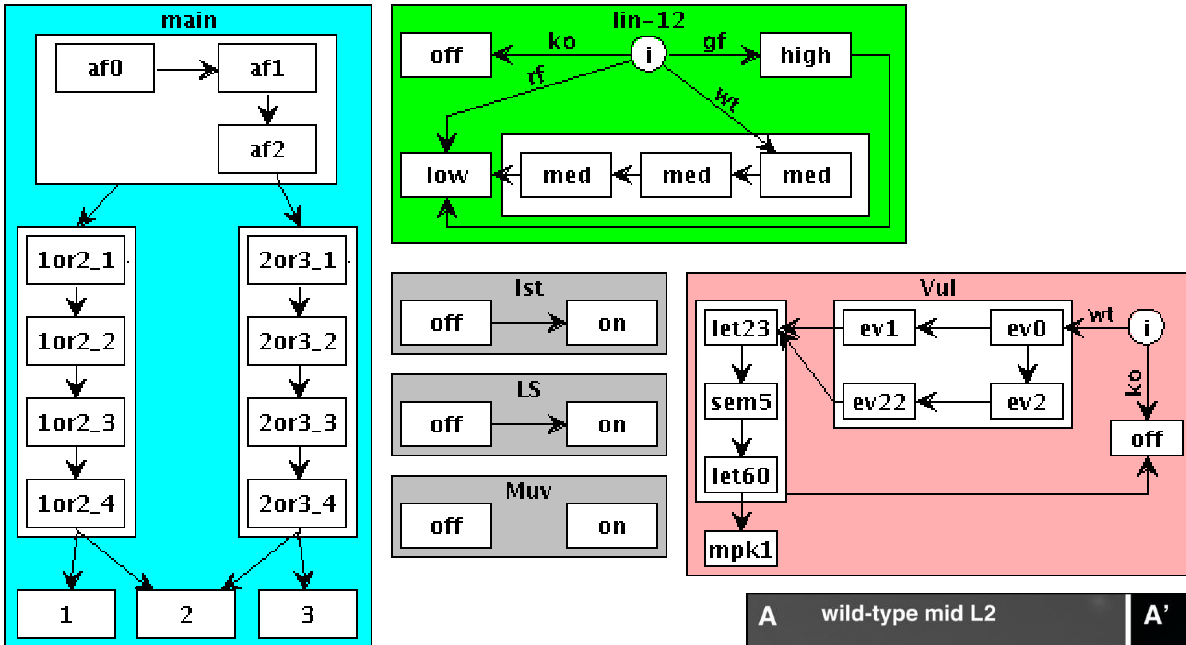
- Variables ranging over (small) finite domains.
- Algebraic update functions.
- Variables change by at most 1 either up or down.
- All variables updated simultaneously.
- Result:
  - Deterministic
  - Synchronous
- Analysis:
  - Simulations
  - Global analysis: stabilization, temporal properties

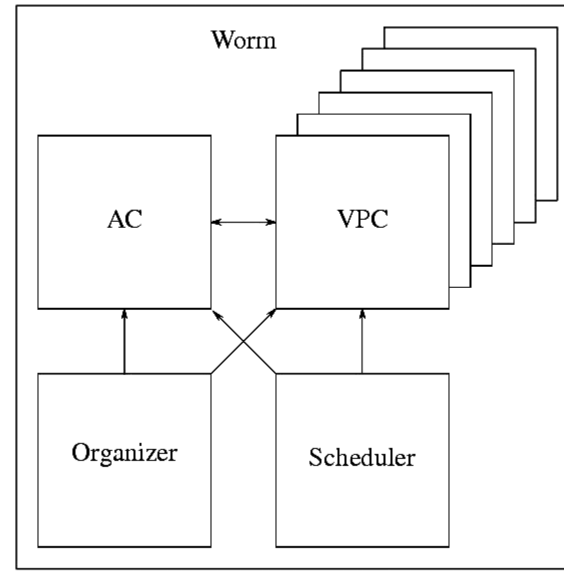
Bounded LTL model checking

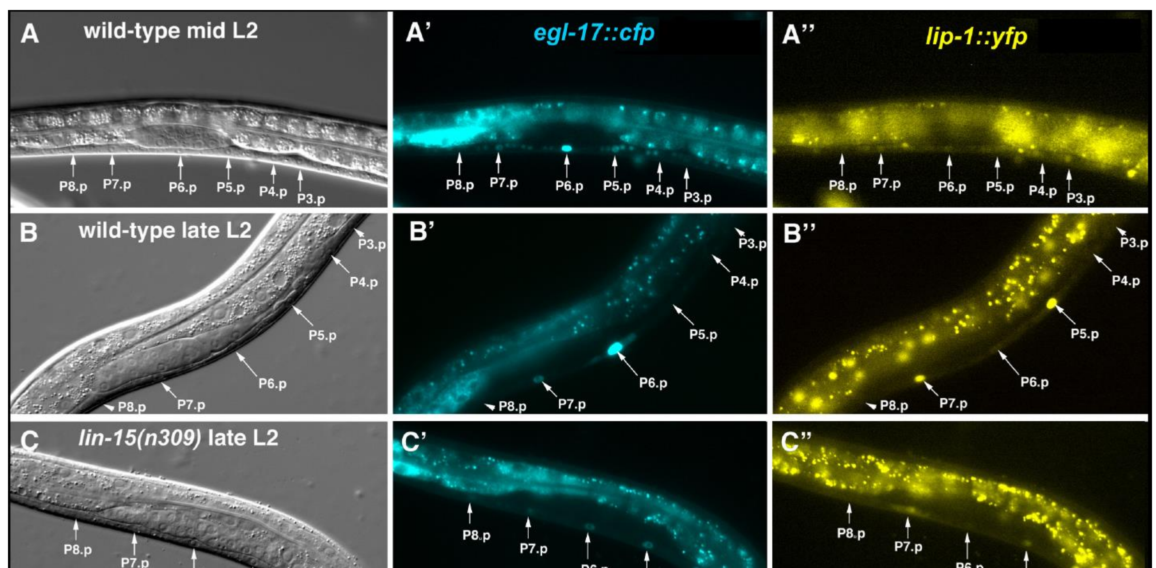


Claessen et al. *CAV 2013*

Cell-cell Communication







Synchronous Composition

- No way to break symmetry.
- Identical processes go through exactly the same computation.
- In our case:
  - All cells assume same fate.

Asynchronous Composition

- Conflicting requirements:
  - Running in isolation.
  - Chosen repeatedly by scheduler.
- No way to choose the right way to run.

Bounded Asynchrony

- Count the number of steps each cell does.
- Disallow schedules where one cell moves in front of the others.
- Essentially, have a barrier in front of the cells.
- Once all cells reach the barrier, move the barrier forward.

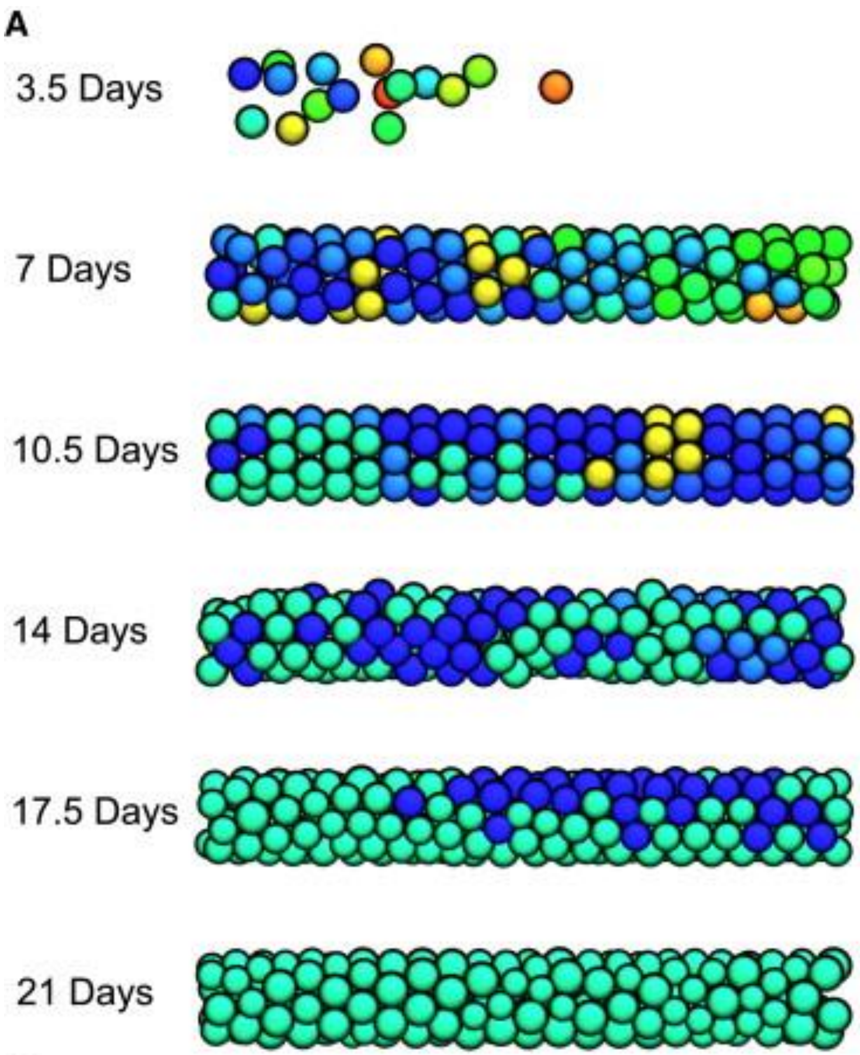
Advantages

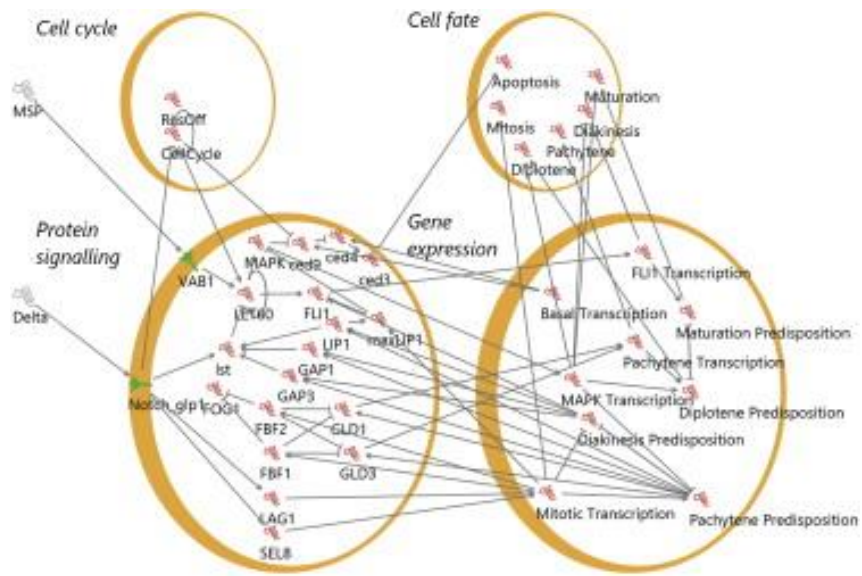
- Asynchrony breaks symmetry.
- Bound breaks the isolation / scheduler dilemma.
- Scheduler allows to concentrate on more important aspects of model.

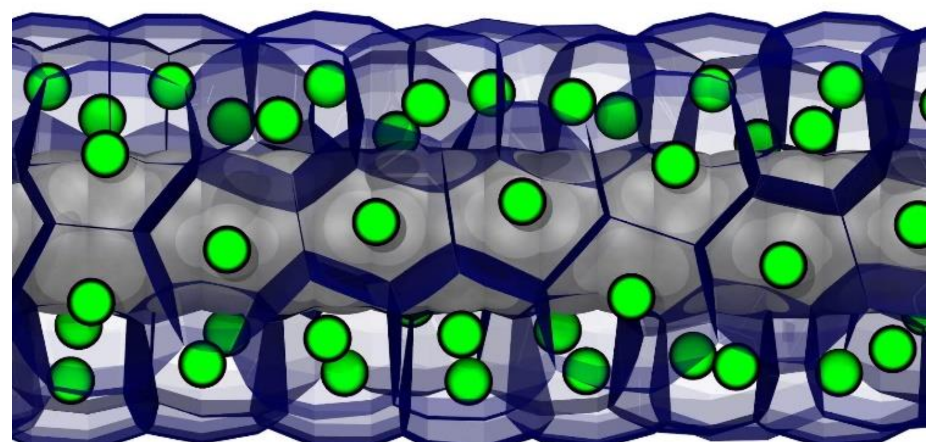
Simulation and Analysis

- Global scheduler allows cells to move separately bounding individual progress.
- In each simulation step:
  - Choose cells that haven't reached barrier.
  - Update these cells together.
- Result:
  - Asynchronous
- Analysis:
  - Simulations
  - Temporal properties

QN+Physical Simulation



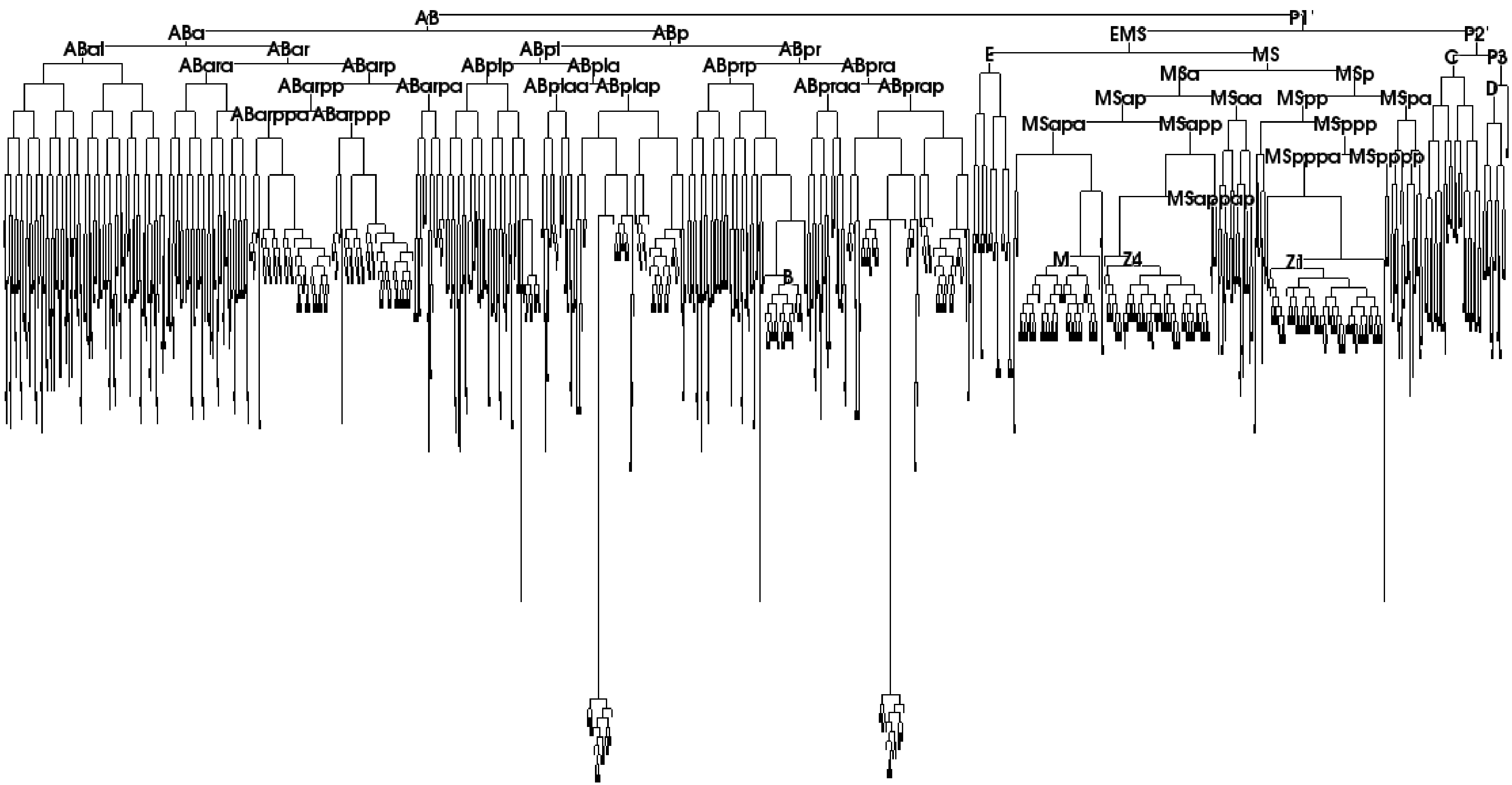




Simulation Details

- Global clock ticks.
- In each simulation step:
  - Update discrete state.
  - Update physical state (or remove for efficiency).
  - Data passes between physical and discrete.
- Result:
  - Stochastic (physical parameters)
  - Synchronous
- Analysis:
  - Simulations
  - Time invariants (physical model) enable global analysis of discrete model

Lineage Computation



Main features

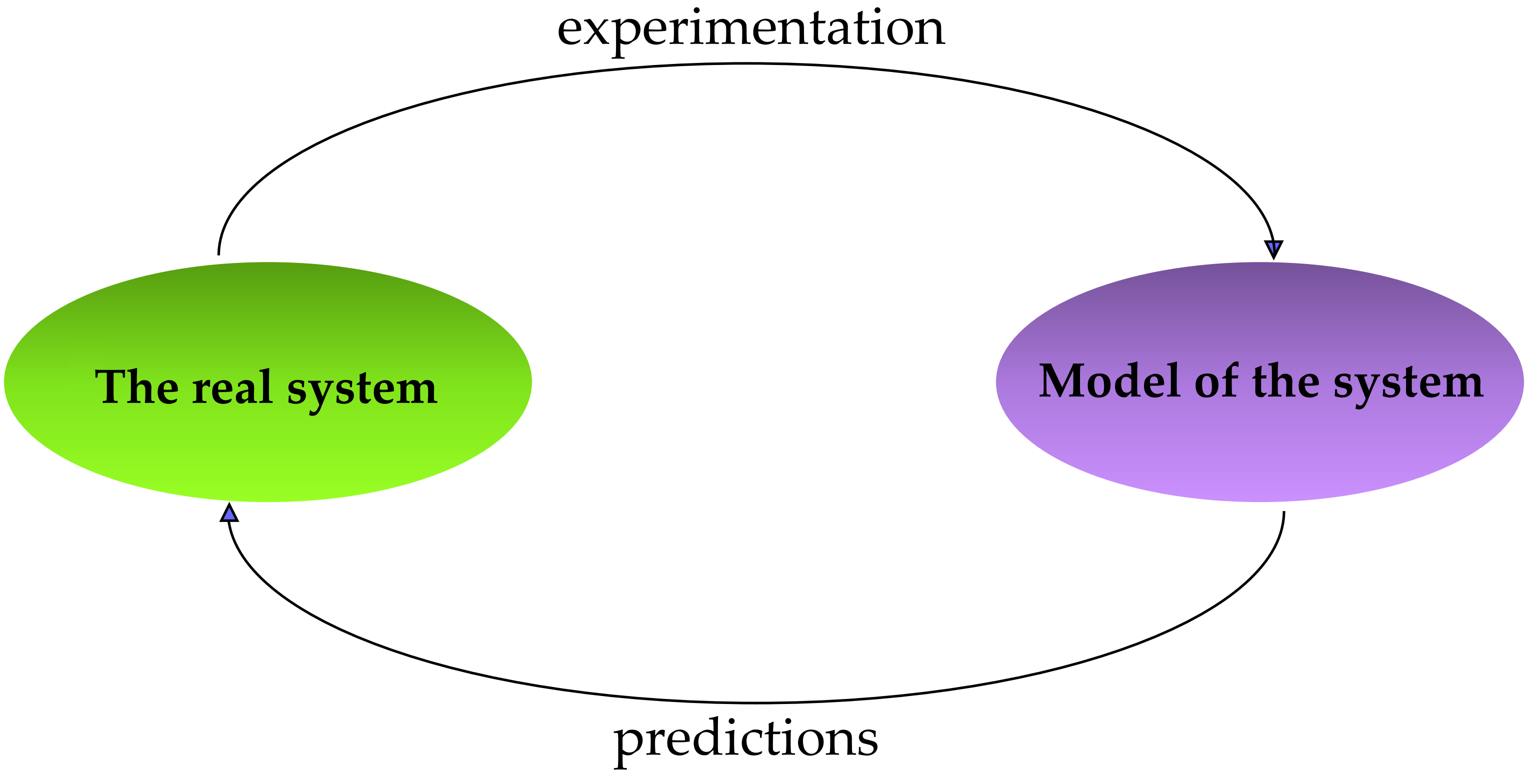
- Each cell type has its own program.
- Transitions:
  - Real time.
  - Change discrete state.
  - Set time for next transition.
  - Possible to divide and initialize other programs.
- No physics (for now).
- Only simulation.

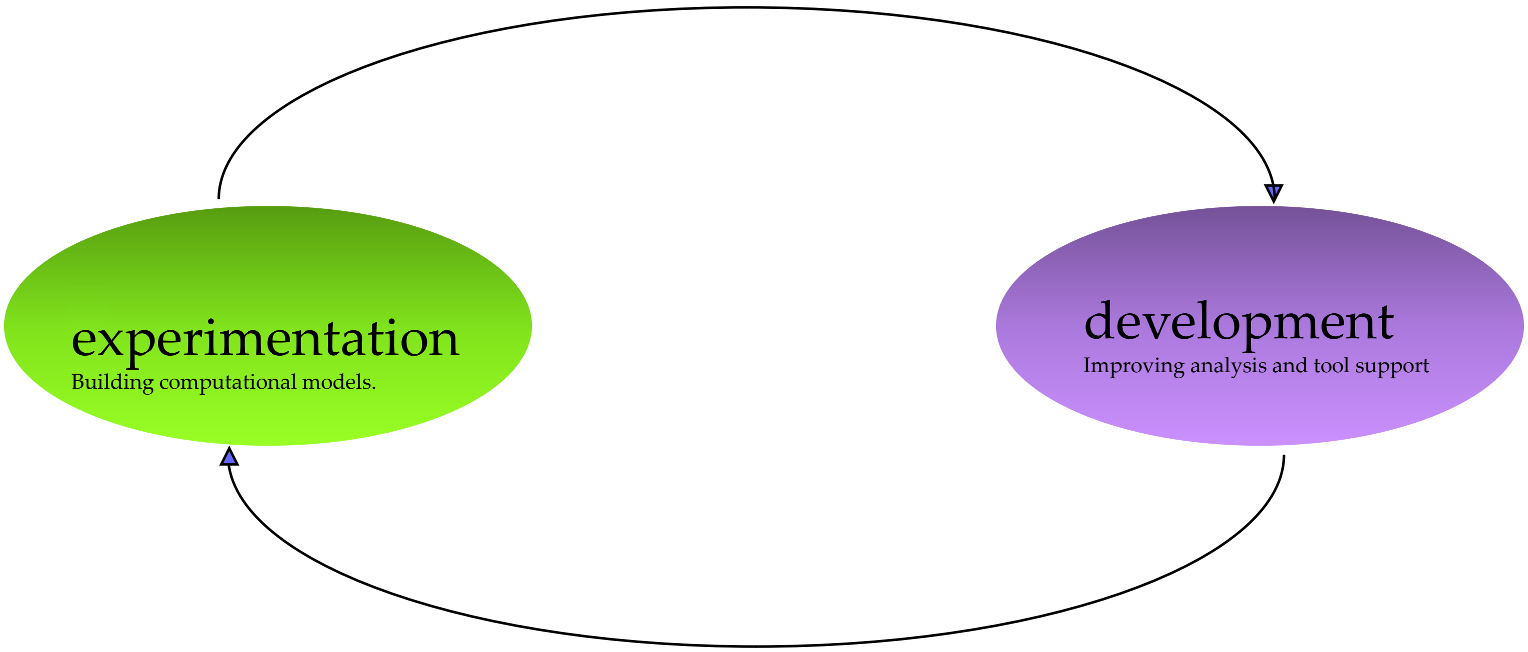
Summary

Timing is everything

- Strict control of individual and global time.
- Synchronous composition rules.
- Additional mechanisms for randomness or breaking symmetry.
- When using, keep asynchrony in check.

Scientific Method




experimentation
Building computational models.
development
Improving analysis and tool support