Qualitative modeling of gene regulatory networks

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MICROCOSME: bacterial systems biology

- **MICROCOSME**: systems biology group at INRIA/Université Grenoble Alpes in Grenoble

  Microbiologists, computer scientists, mathematicians, physicists, …

https://team.inria.fr/microcosme

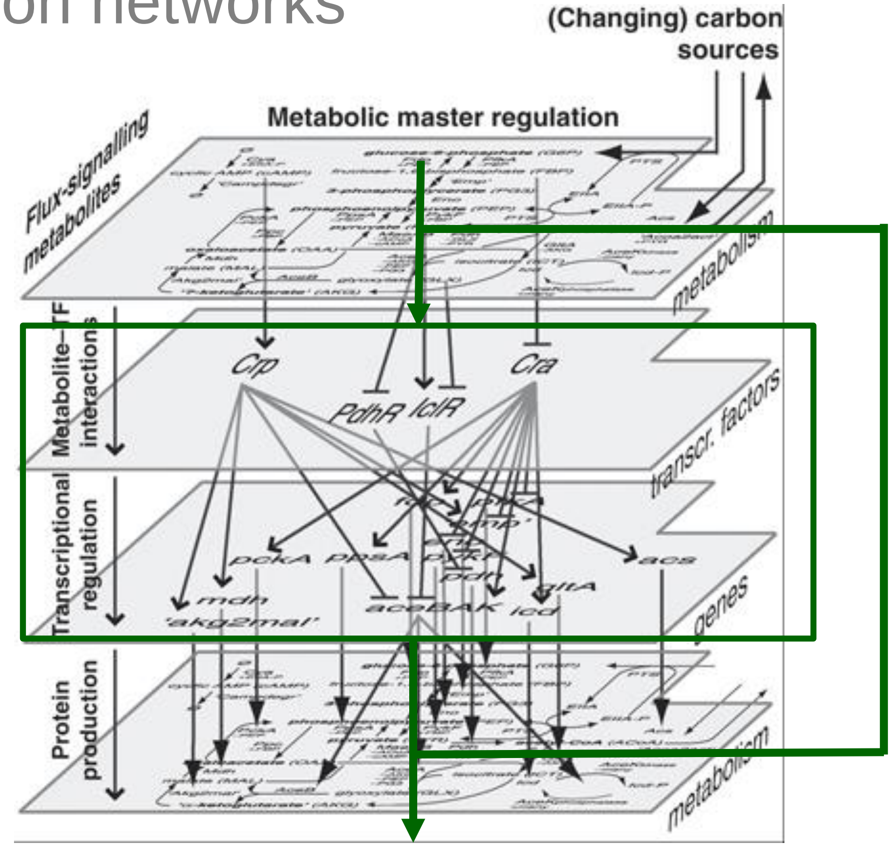
- **Objective:** analysis, engineering, and control of the growth of bacteria
  - Specific research problems shaped by **biological questions**
  - Problems often addressed by combination of **models and experiments**

Overview

- Part 1. Systems biology and kinetic modeling
- Part 2. Metabolic network modeling
- Part 3. Gene regulatory network modeling
  - Quantitative modeling of gene regulatory networks
  - **Qualitative modeling of gene regulatory networks**
  - Stochastic modeling of gene regulatory networks
  - Practical on integrated models of bacterial growth (Matlab)

Gene regulatory networks

- Focus on **subsystems** that can be studied in isolation due to **modular structure** of reaction networks
  - Time-scale hierarchies
  - Connectivity structure
- **Gene regulatory networks**
  - Genes, proteins, and regulatory interactions
  - Reactions involved in transcription and translation and their regulation
  - Time-scale: min (mRNA) to h (proteins)



Kotte *et al.* (2010), *Mol. Syst. Biol.*, 6: 355

Modeling of gene regulatory networks

- Well-established theory for modeling of gene regulatory networks using ordinary differential equation (ODE) models

  Bolouri (2008), *Computational Modeling of Gene Regulatory Networks*, Imperial College Press

  Polynikis *et al.* (2009), *J. Theor. Biol.*, 261(4):511-30

- Practical problems encountered by modelers:
  - Knowledge on molecular mechanisms rare
  - Quantitative information on kinetic parameters and molecular concentrations absent
  - Large models

Qualitative modeling and simulation

- Intuition: essential properties of network dynamics **robust** against reasonable model simplifications
- **Qualitative** modeling and simulation of large and complex gene regulatory networks using **simplified ODE models**

  de Jong, Gouzé *et al.* (2004), *Bull. Math. Biol.*, 66(2):301-40

- Close proximity with **discrete, logical models** of gene regulation

  Thomas and d'Ari (1990), *Biological Feedback*, CRC Press

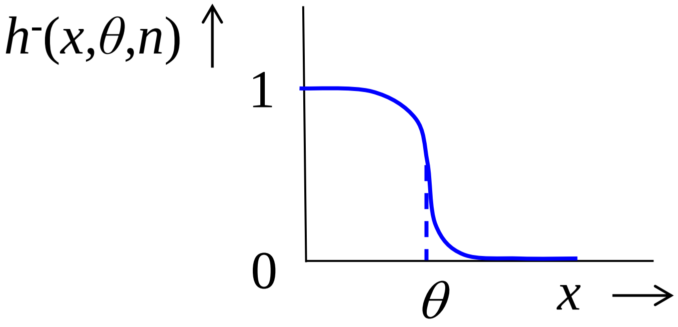
  Kauffman (1993), *The Origins of Order*, Oxford University Press

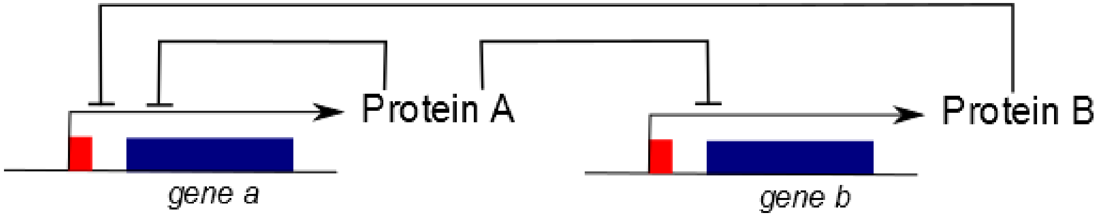
Ordinary differential equation models

- Gene regulatory networks modeled by ODE models using **sigmoid functions** to describe regulatory interactions

$$\dot{x}_a = \kappa_a\, h^-(x_a, \theta_{a2}, n)\, h^-(x_b, \theta_b, n) - \gamma_a\, x_a$$

$$\dot{x}_b = \kappa_b\, h^-(x_a, \theta_{a1}, n) - \gamma_b\, x_b$$





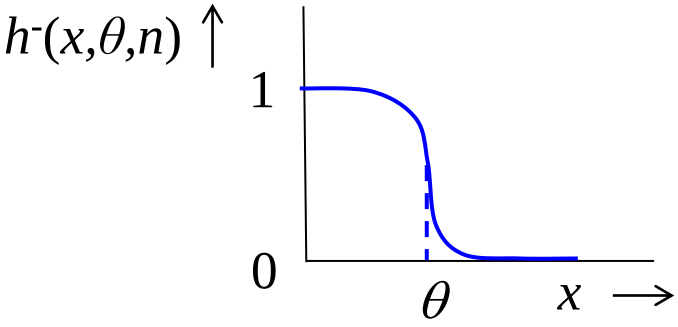
x : protein concentration
θ : threshold concentration
κ , γ : rate constants
n : steepness parameter

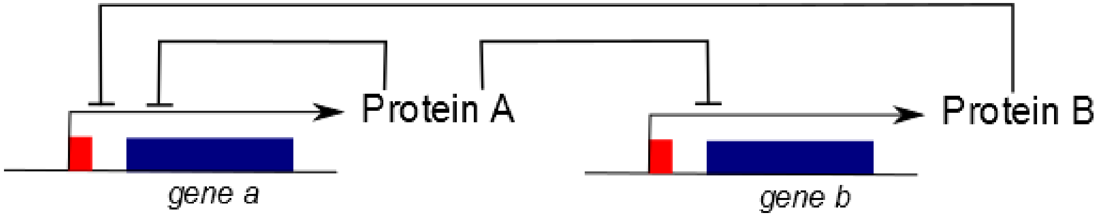
- Question: Write variant of model where A and B jointly repress expression of gene *a*

Ordinary differential equation models

- Gene regulatory networks modeled by ODE models using **sigmoid functions** to describe regulatory interactions

$$\dot{x}_a = \kappa_a \, h^-(x_a, \theta_{a2}, n) \, h^-(x_b, \theta_b, n) - \gamma_a \, x_a$$
$$\dot{x}_b = \kappa_b \, h^-(x_a, \theta_{a1}, n) - \gamma_b \, x_b$$





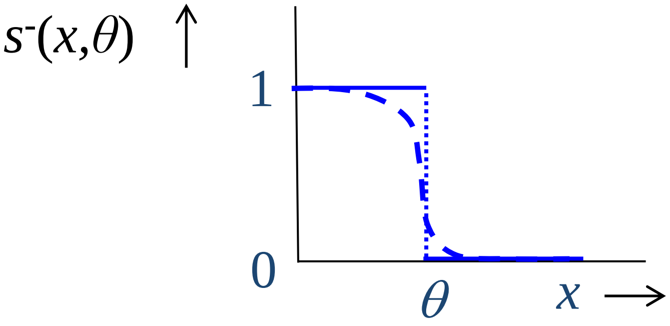
x : protein concentration
θ : threshold concentration
κ , γ : rate constants
n : steepness parameter

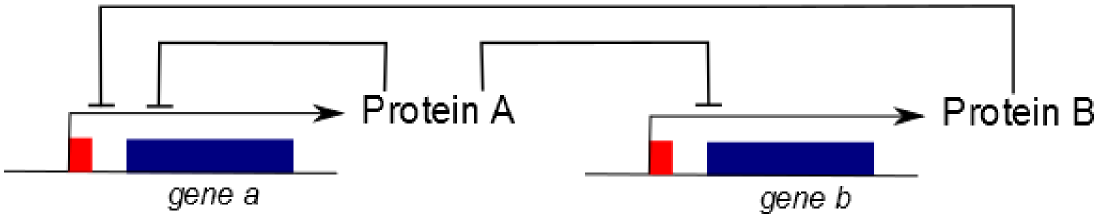
- Expressions of sigmoid functions account for **combinatorial control** of gene expression (AND, OR, NOR, …)

PL differential equation models

- ODE models approximated by means of **step functions** to describe regulatory interactions

$$\dot{x}_a = \kappa_a\, s^-(x_a,\theta_{a2})\, s^-(x_b,\theta_b) - \gamma_a\, x_a$$
$$\dot{x}_b = \kappa_b\, s^-(x_a,\theta_{a1}) - \gamma_b\, x_b$$





x : protein concentration
θ : threshold concentration
κ, γ : rate constants

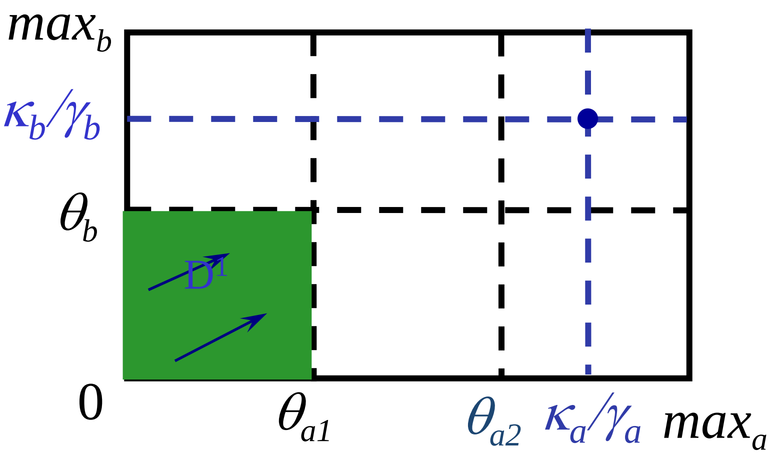
- Piecewise-linear (PL)DE models of gene regulatory networks

Glass and Kauffman (1973), *J. Theor. Biol.*, 39(1):103-29

Mathematical analysis of PL models

- Analysis of local dynamics of PL models

  Monotone convergence towards **focal point** in regions separated by thresholds



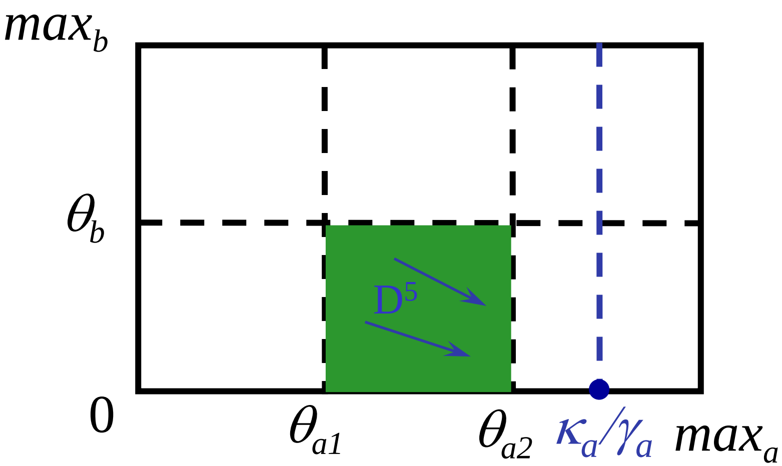
$$\dot{x}_a = \kappa_a - \gamma_a x_a$$
$$\dot{x}_b = \kappa_b - \gamma_b x_b$$

$$\dot{x}_a = \kappa_a\, s^-(x_a, \theta_{a2})\, s^-(x_b, \theta_b) - \gamma_a x_a$$
$$\dot{x}_b = \kappa_b\, s^-(x_a, \theta_{a1}) - \gamma_b x_b$$

Glass and Kauffman (1973), *J. Theor. Biol.*, 39(1):103-29

Mathematical analysis of PL models

- Analysis of local dynamics of PL models
  - Monotone convergence towards **focal point** in regions separated by thresholds



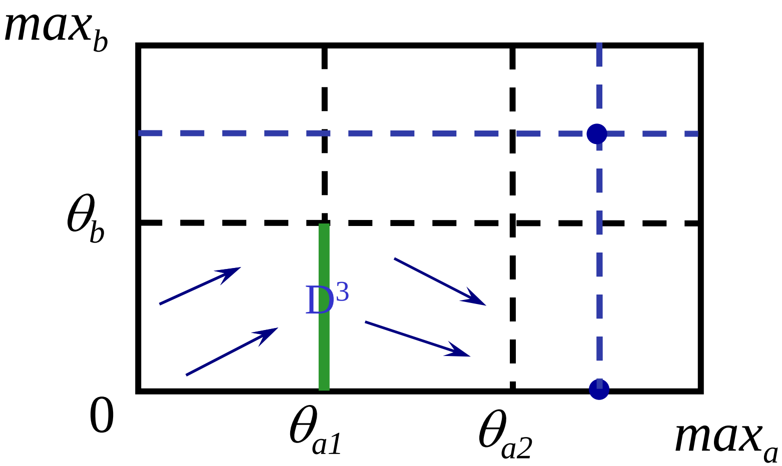
$$\dot{x}_a = \kappa_a - \gamma_a\, x_a$$
$$\dot{x}_b = -\, \gamma_b\, x_b$$

$$\dot{x}_a = \kappa_a\, s^-(x_a, \theta_{a2})\, s^-(x_b, \theta_b) - \gamma_a\, x_a$$
$$\dot{x}_b = \kappa_b\, s^-(x_a, \theta_{a1}) - \gamma_b\, x_b$$

Glass and Kauffman (1973), *J. Theor. Biol.*, 39(1):103-29

Mathematical analysis of PL models

- Analysis of local dynamics of PL models
  - Instantaneous crossing of regions located on thresholds, or …



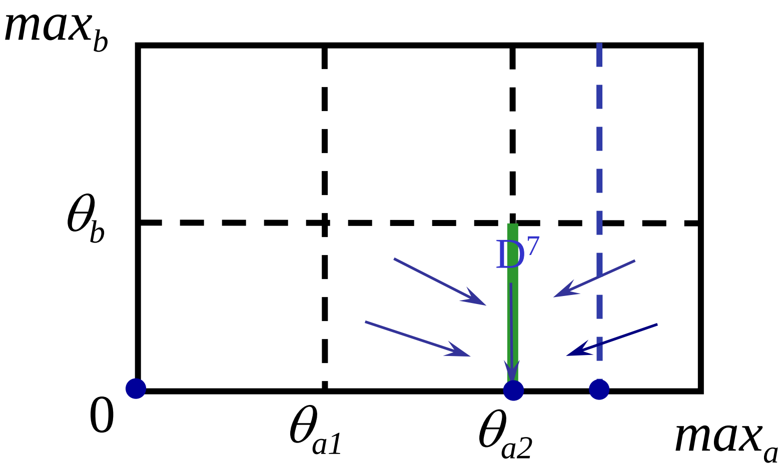
$$\dot{x}_a = \kappa_a \, s^-(x_a, \theta_{a2}) \, s^-(x_b, \theta_b) - \gamma_a \, x_a$$

$$\dot{x}_b = \kappa_b \, s^-(x_a, \theta_{a1}) - \gamma_b \, x_b$$

Mathematical analysis of PL models

- Analysis of local dynamics of PL models

  … quasi-monotone convergence towards **focal sets** located on threshold hyperplanes



$$\dot{x}_a = \kappa_a\, s^-(x_a, \theta_{a2})\, s^-(x_b, \theta_b) - \gamma_a\, x_a$$
$$\dot{x}_b = \kappa_b\, s^-(x_a, \theta_{a1}) - \gamma_b\, x_b$$

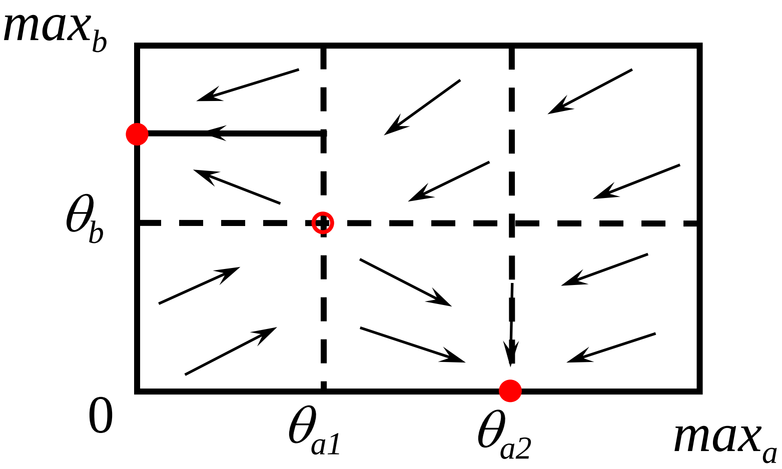
- Extension of PL differential **equations** to differential **inclusions** using Filippov approach

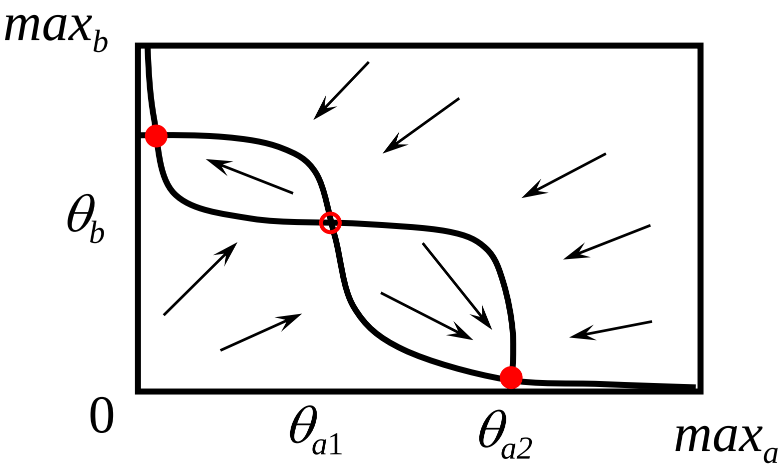
Gouzé and Sari (2002), *Dyn. Syst.*, 17(4):299-316

Qualitative analysis of PL models

- Analysis of global dynamics obtained by piecing together local dynamics in regions

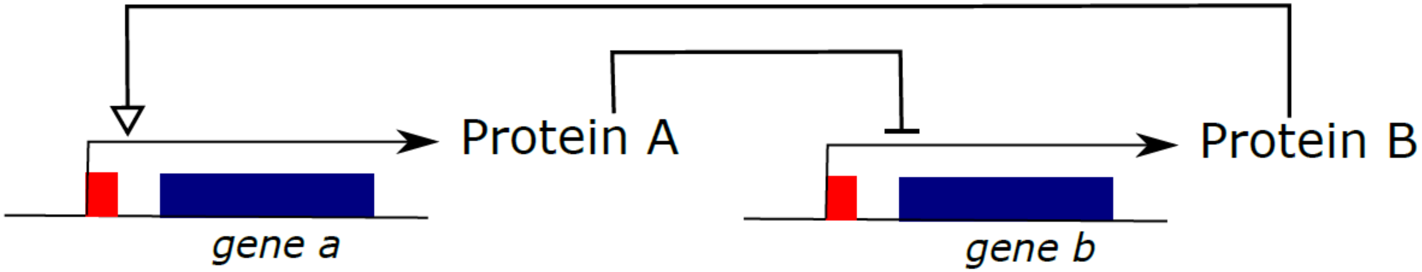
  PL approximation preserves bistability of cross-inhibition network





Simple oscillator network

- Question: write out the PLDE model for a simple oscillator network



- Question: perform phase space analysis of PLDE model

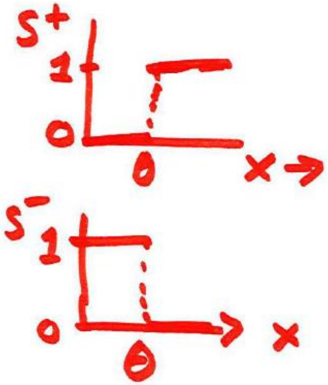
Polynikis *et al.* (2009), *J. Theor. Biol.*, 261:511-530

Simple oscillator network

- Question: write out the PLDE model for a simple oscillator network

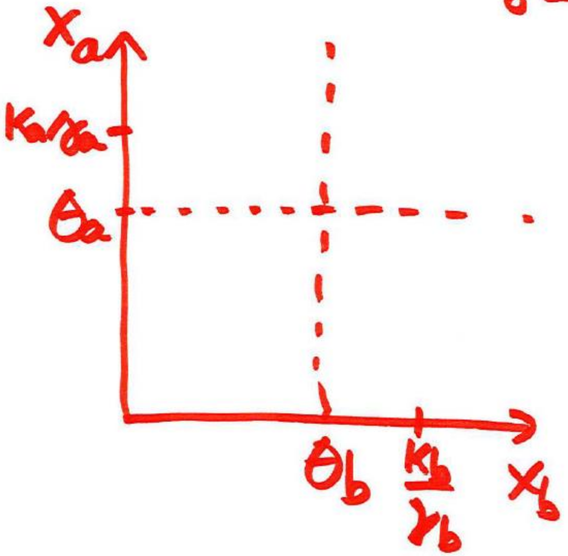
$$\dot{x}_a = K_a\, s^+(x_b, \theta_b) - \gamma_a x_a$$

$$\dot{x}_b = K_b\, s^-(x_a, \theta_a) - \gamma_b x_b$$



$$\frac{K_a}{\gamma_a} > \theta_a$$

$$\frac{K_b}{\gamma_b} > \theta_b$$



Simple oscillator network

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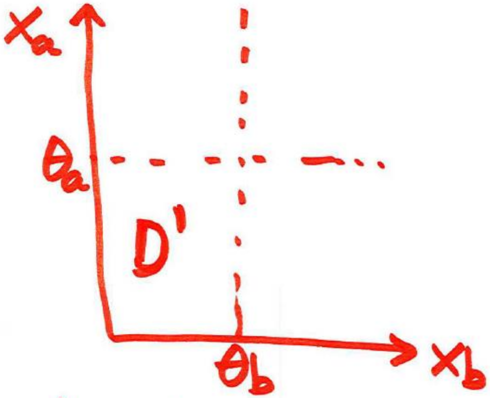
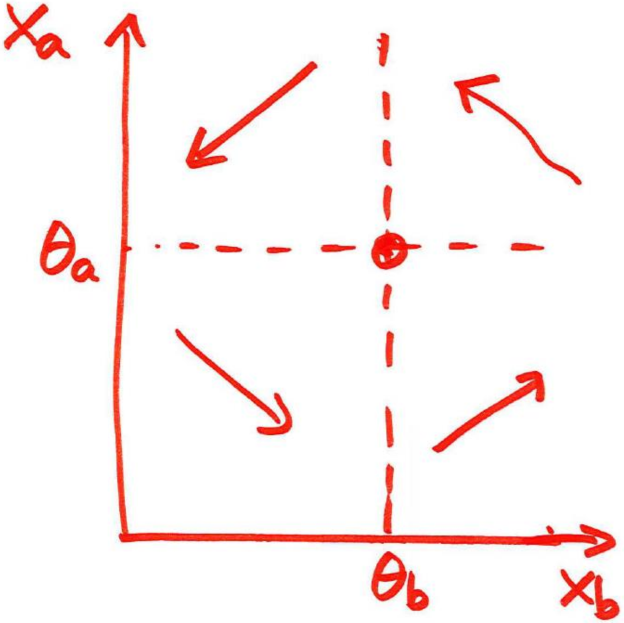


D': $\dot{x}_a = -\gamma_a x_a$

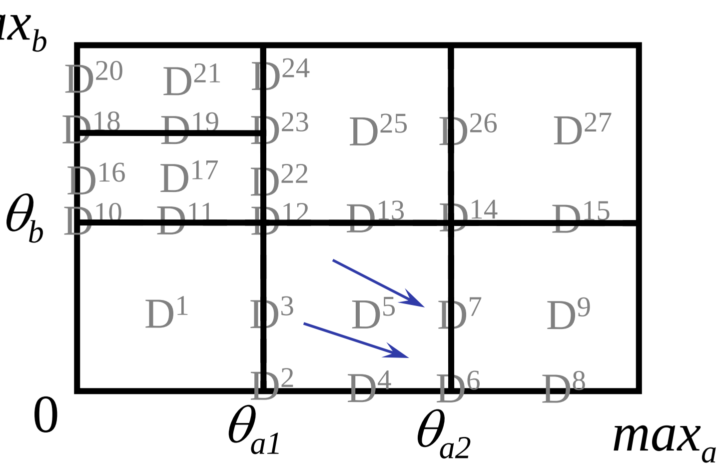
$\dot{x}_b = k_b - \gamma_b x_b$



Qualitative analysis of PL models

- State space can be partitioned into regions with **unique** derivative sign pattern
- **Qualitative abstraction** yields state transition graph that provides discrete picture of continuous dynamics

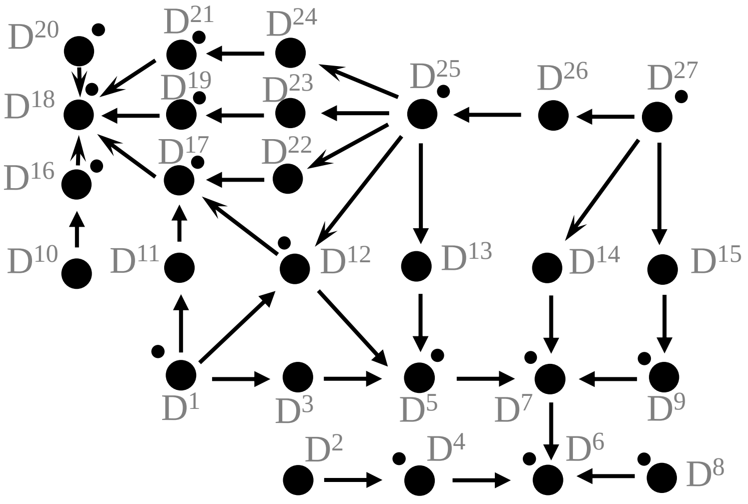
Alur *et al.* (2000), *Proc. IEEE*, 88(7):971-84



D5: $\dot{x}_a > 0$
$\dot{x}_b < 0$

de Jong *et al.* (2004), *Bull. Math. Biol.*, 66(2):301-40

Batt *et al.* (2008), *Automatica*, 44(4):982-9



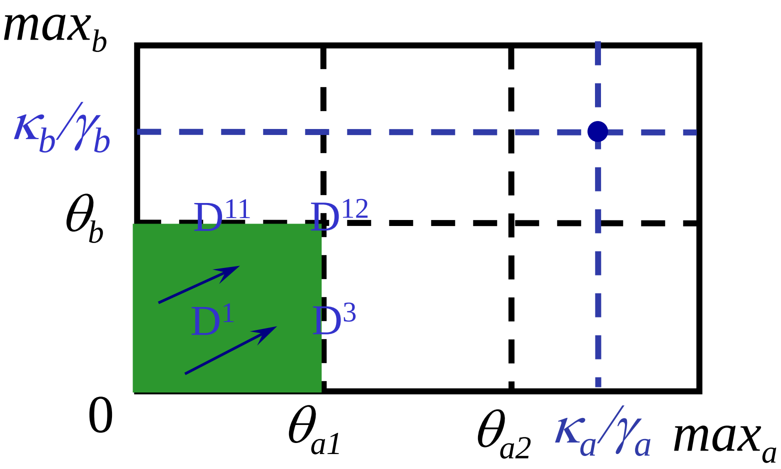
D1: $\dot{x}_a > 0$
$\dot{x}_b > 0$

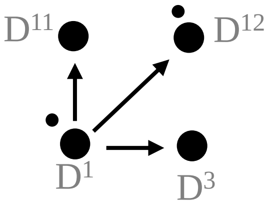
D5: $\dot{x}_a > 0$
$\dot{x}_b < 0$

D7: $\dot{x}_a = 0$
$\dot{x}_b < 0$

Qualitative analysis of PL models

- State transition graph gives **conservative approximation** of continuous dynamics
  - Every solution of PL model corresponds to path in state transition graph
  - Converse is not necessarily true!
- State transition graph is **invariant** for given inequality constraints on parameters





$$0 < \theta_{a1} < \theta_{a2} < \kappa_a/\gamma_a < max_a$$

$$0 < \theta_b < \kappa_b/\gamma_b < max_b$$

Batt *et al.* (2008), *Automatica*, 44(4):982-9

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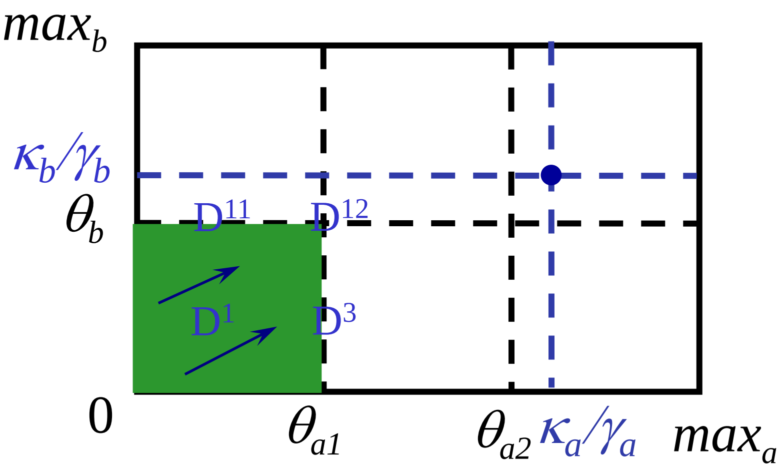

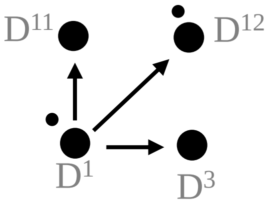

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Batt *et al.* (2008), *Automatica*, 44(4):982-9

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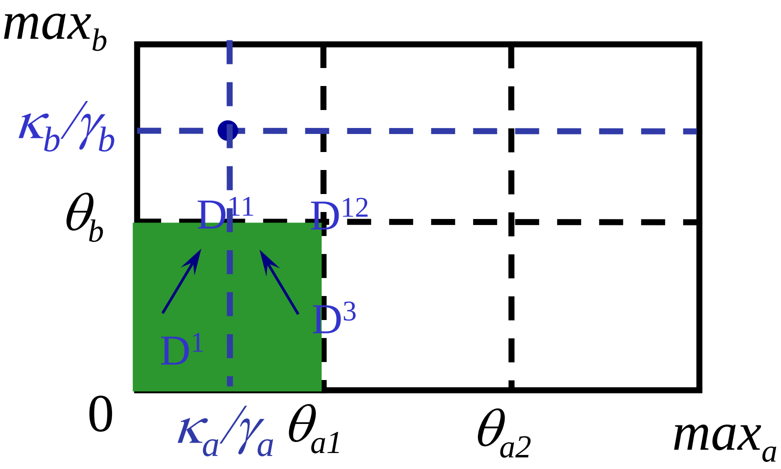
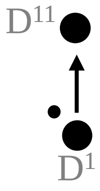




$$0 < \kappa_a/\gamma_a < \theta_{a1} < \theta_{a2} < max_a$$

$$0 < \theta_b < \kappa_b/\gamma_b < max_b$$

Batt *et al.* (2008), *Automatica*, 44(4):982-9

Use of state transition graph

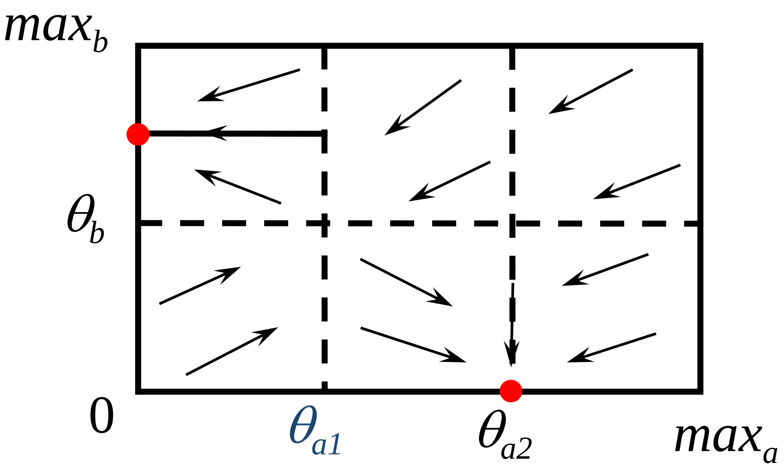
- Analysis of **steady states** and **limit cycles** of PL models
  - Attractor states in graph correspond (under certain conditions) to stable steady states of PL model

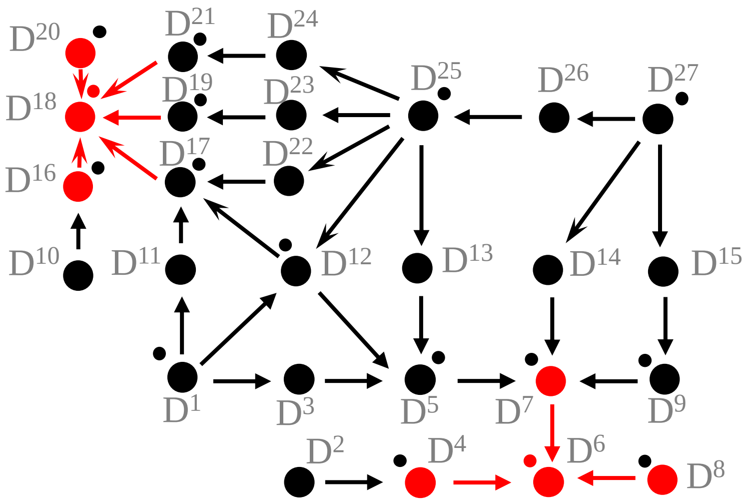
Casey *et al.* (2006), *J. Math Biol.*, 52(1):27-56

  - Attractor cycles in graph correspond (under certain conditions) to stable limit cycles of PL model

Glass and Pasternack (1978), *J. Math Biol.*, 6(2):207-23

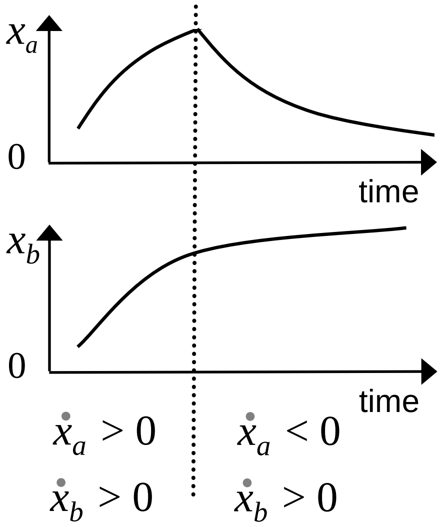
Edwards (2000), *Physica D*, 146(1-4):165-99





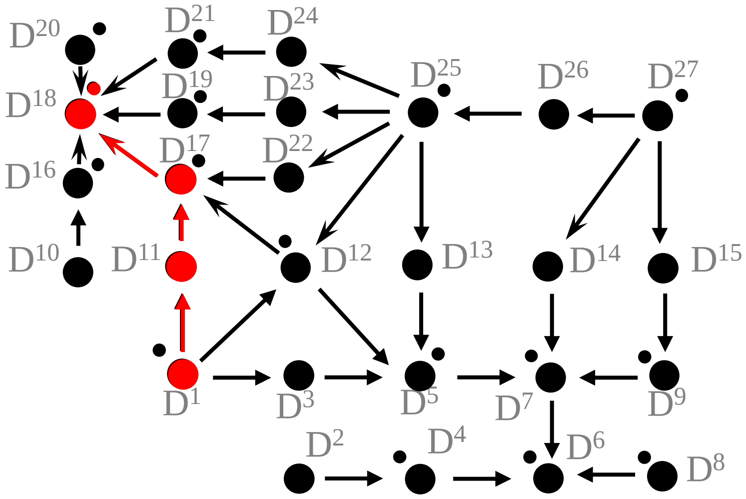
Use of state transition graph

- Paths in state transition graph represent predicted sequences of qualitative events
- **Model validation**: comparison of predicted and observed sequences of qualitative events



Concistency?

Yes



D^1: $\dot{x}_a > 0$, $\dot{x}_b > 0$

D^{17}: $\dot{x}_a < 0$, $\dot{x}_b > 0$

D^{18}: $\dot{x}_a = 0$, $\dot{x}_b = 0$

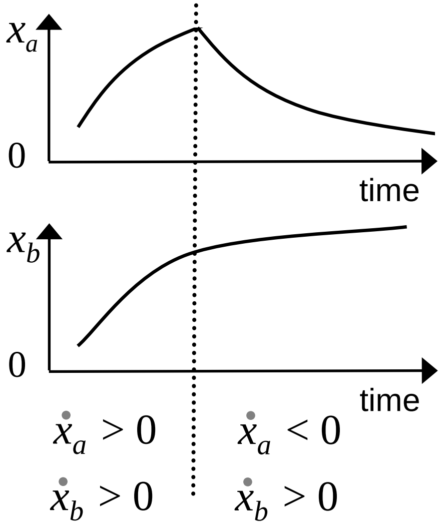
- Need for automated and efficient tools for model validation

Model validation by model checking

- Dynamic properties of system can be expressed in **temporal logic** (CTL)

There Exists a Future state where $\dot{x}_a > 0$ and $\dot{x}_b > 0$
and starting from that state,
there Exists a Future state where $\dot{x}_a < 0$ and $\dot{x}_b > 0$

$$EF(\dot{x}_a > 0 \wedge \dot{x}_b > 0 \wedge EF(\dot{x}_a < 0 \wedge \dot{x}_b > 0))$$

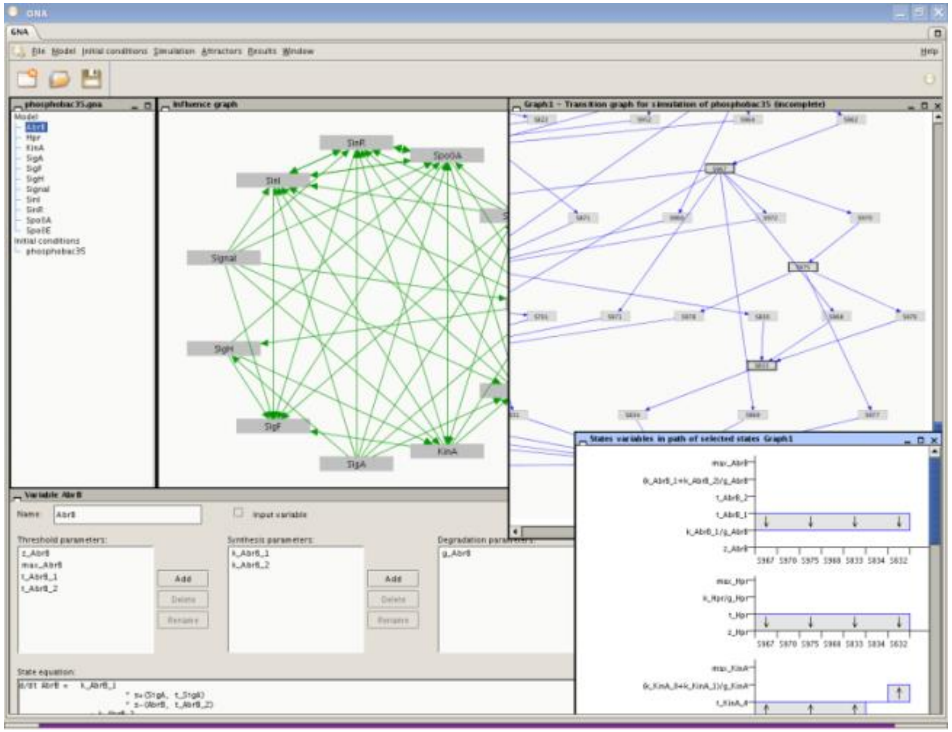


- **Model checking** is automated technique for verifying that state transition graph satisfies temporal-logic statements
  - Efficient computer tools available for model checking

Batt *et al.* (2005), *Bioinformatics*, 21(supp. 1): i19-i28

Genetic Network Analyzer (GNA)

- Qualitative analysis of PL models implemented in Java: **Genetic Network Analyzer (GNA)**



Genostar

bioinformatics solutions

de Jong *et al.* (2003),
Bioinformatics, 19(3):336-44

http://www-helix.inrialpes.fr/gna

Genetic Network Analyzer (GNA)

- Model-checking technology made available to GNA user
  - Develop temporal logics tailored to biological questions

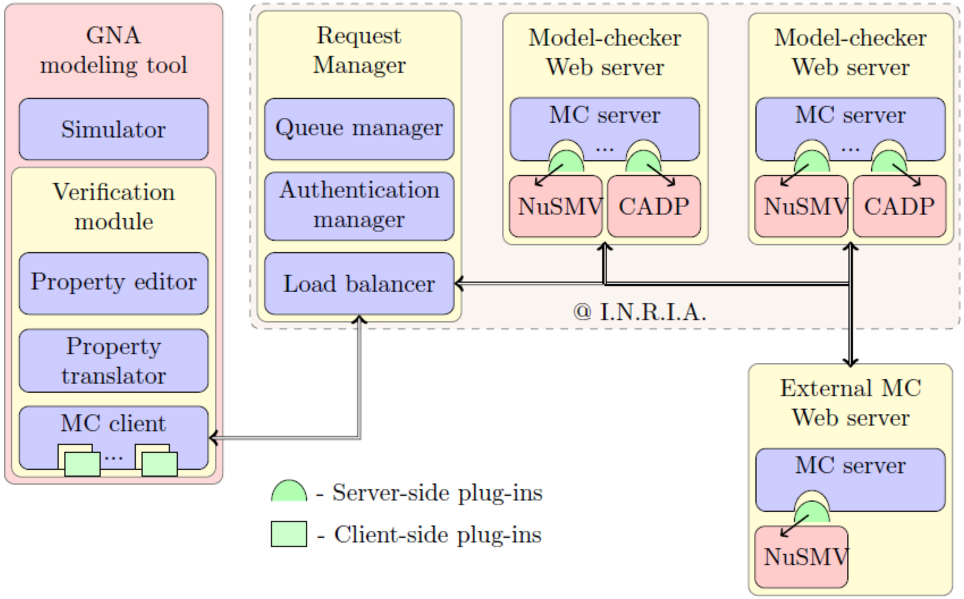
    Mateescu *et al.* (2011), *Theor. Comput. Sci.*, 412:2854-83

  - Develop temporal-logic patterns for frequently-asked modeling questions

    Monteiro *et al.* (2008), *Bioinformatics*, 24(16):i227-33

  - Connect GNA to standard model checkers through a web-server connection

    Monteiro *et al*., (2009), *BMC Bioinform.*, 10:450



Analysis of bacterial regulatory networks

- Applications of qualitative simulation in bacteria:
  - Initiation of sporulation in *Bacillus subtilis*

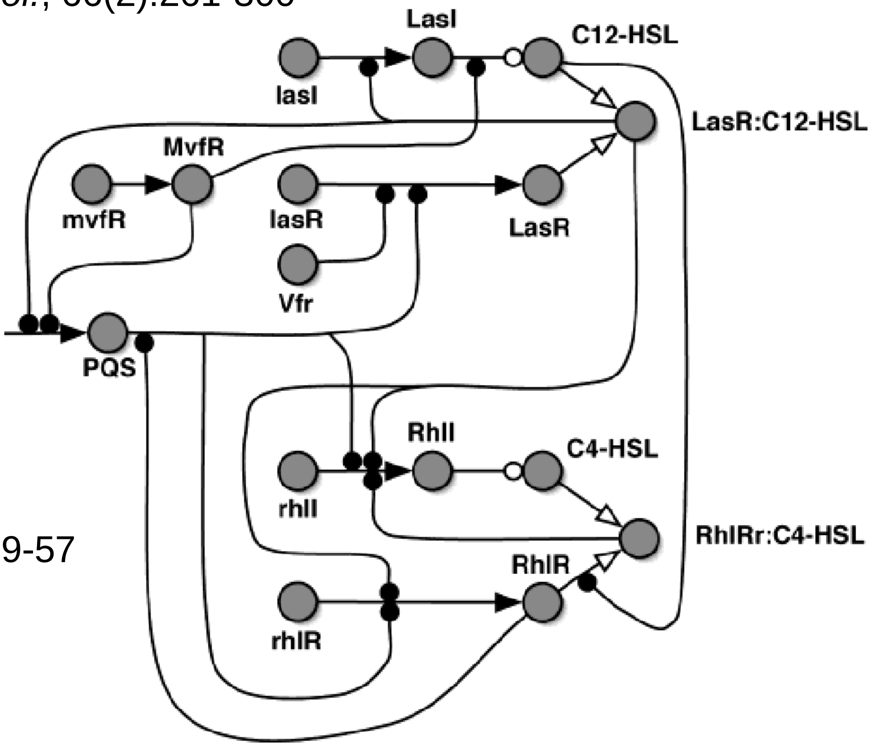
    de Jong, Geiselmann *et al.* (2004), *Bull. Math. Biol.*, 66(2):261-300

  - Quorum sensing in *Pseudomonas aeruginosa*

    Viretta and Fussenegger (2004), *Biotechnol. Prog.*, 20(3):670-8

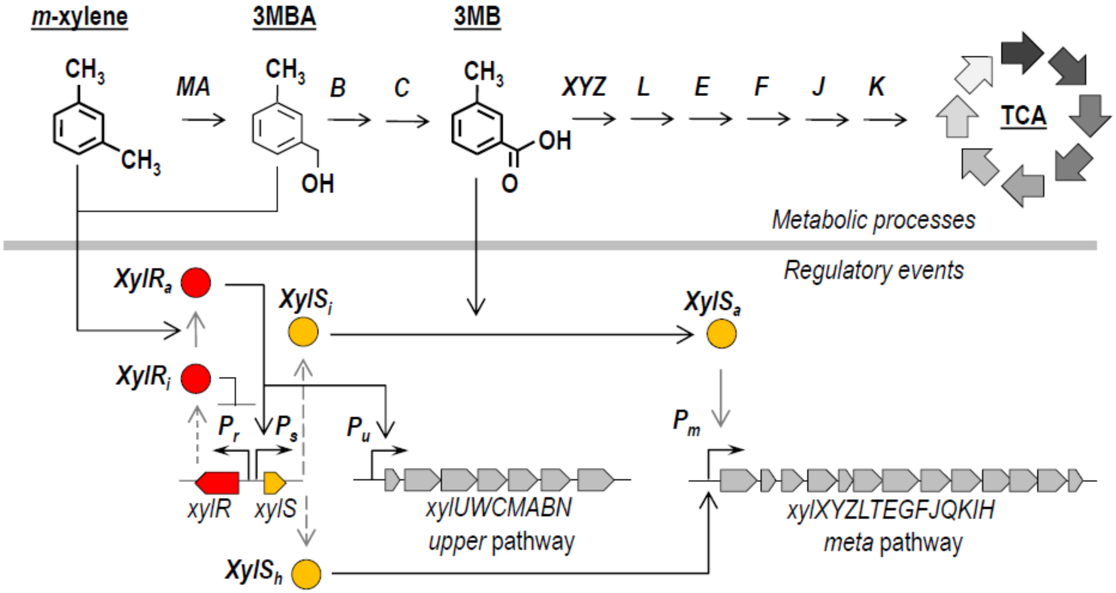
  - Onset of virulence in *Erwinia chrysanthemi*

    Sepulchre *et al.* (2007), *J. Theor. Biol.*, 244(2):239-57



Biodegradation of pollutants by *P. putida*

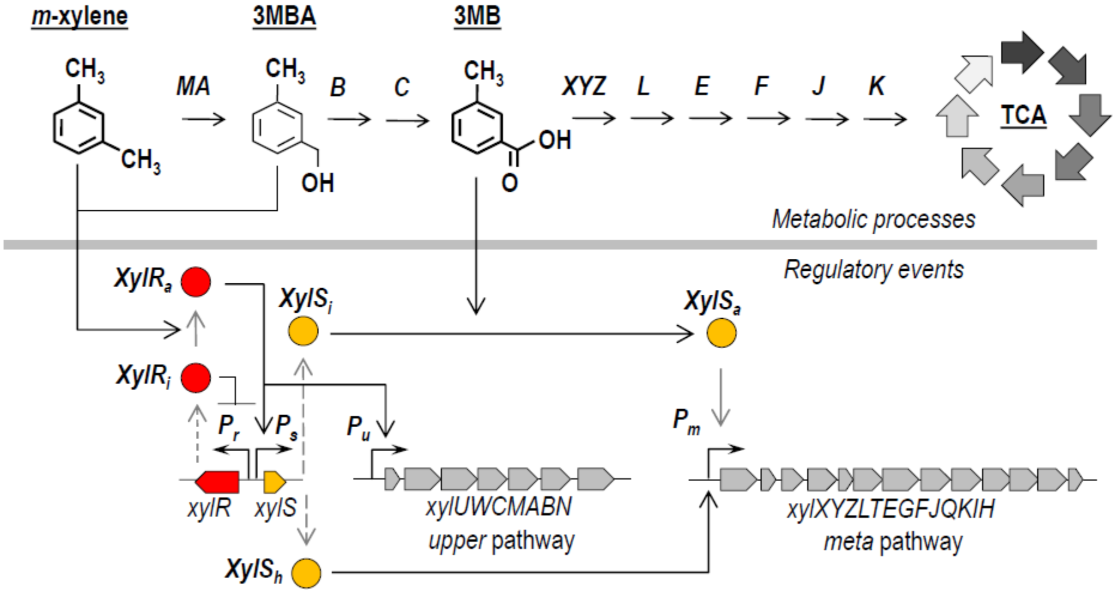
- Soil bacterium *Pseudomonas putida* mt-2 is archetypal model for environmental biodegradation of aromatic pollutants
  - TOL network involved in degradation of *m*-xylene to intermediates for central carbon metabolism



Rocha-Silva *et al.* (2011), *Environ. Microbiol.*, 13(9):2389-402

Role of regulators of TOL network

- **Question**: what is the role of the central, plasmid-encoded regulators XylR and XylS?



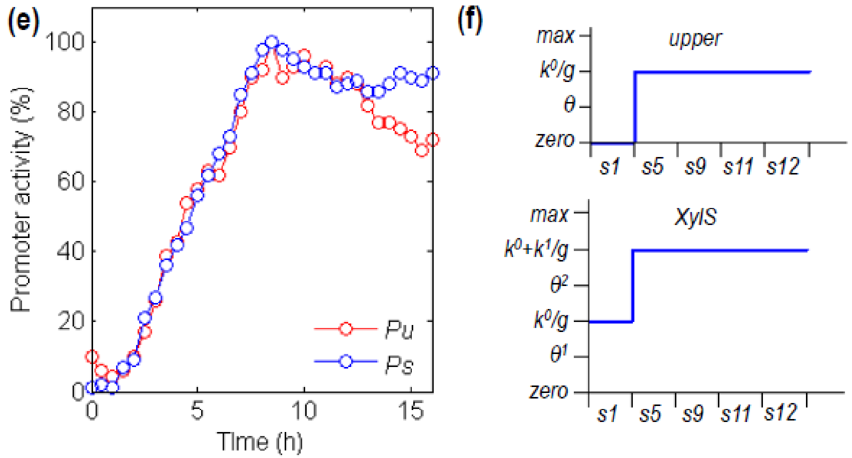
- Development of PL model of TOL network

  Translation of network diagram into regulatory logic and PL model

Rocha-Silva *et al.* (2011), *BMC Syst. Biol.*, 5:191

Role of regulators of TOL network

- Validation of model by testing predictions under different perturbation conditions (mutants, metabolic inducers, …)

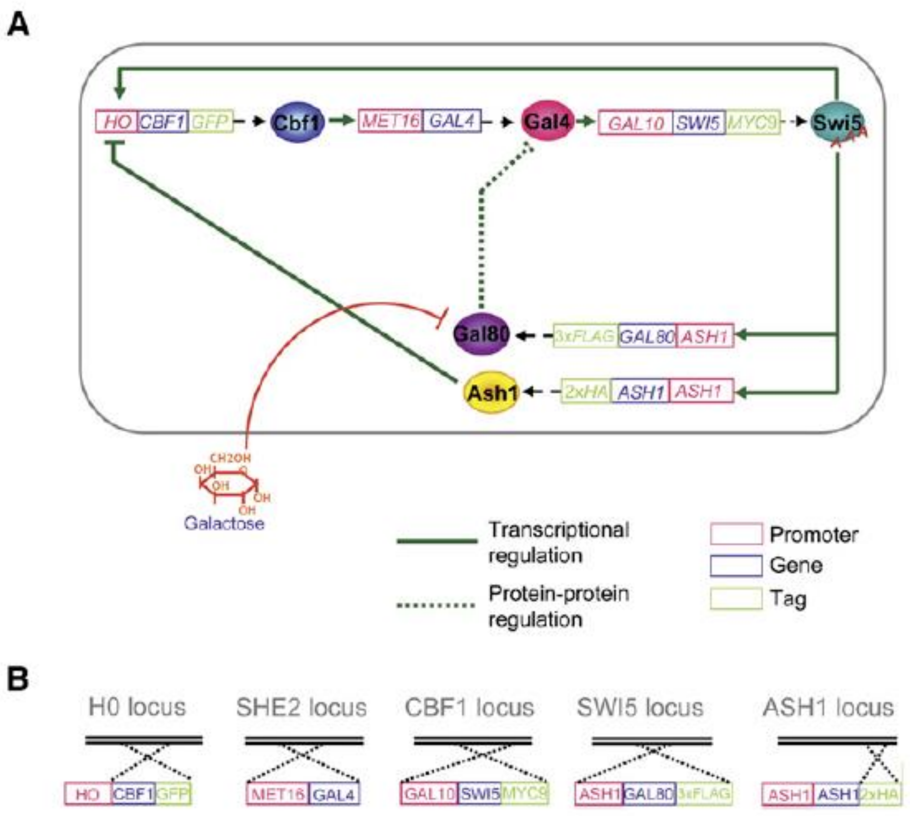


- Plasmid-encoded regulators of TOL network act as **regulatory firewall**
  - Prevent toxic *m*-xylene and its biodegradation intermediates from intervening with indigenous metabolic pathways

Rocha-Silva *et al.* (2011), *BMC Syst. Biol.*, 5:191

IRMA: synthetic network in yeast

- **IRMA**: synthetic network in yeast consisting of interlocked positive and negative feedback loops
    - Networks functions independently from host cell
- Network can be externally controlled by growing cells in glucose or galactose

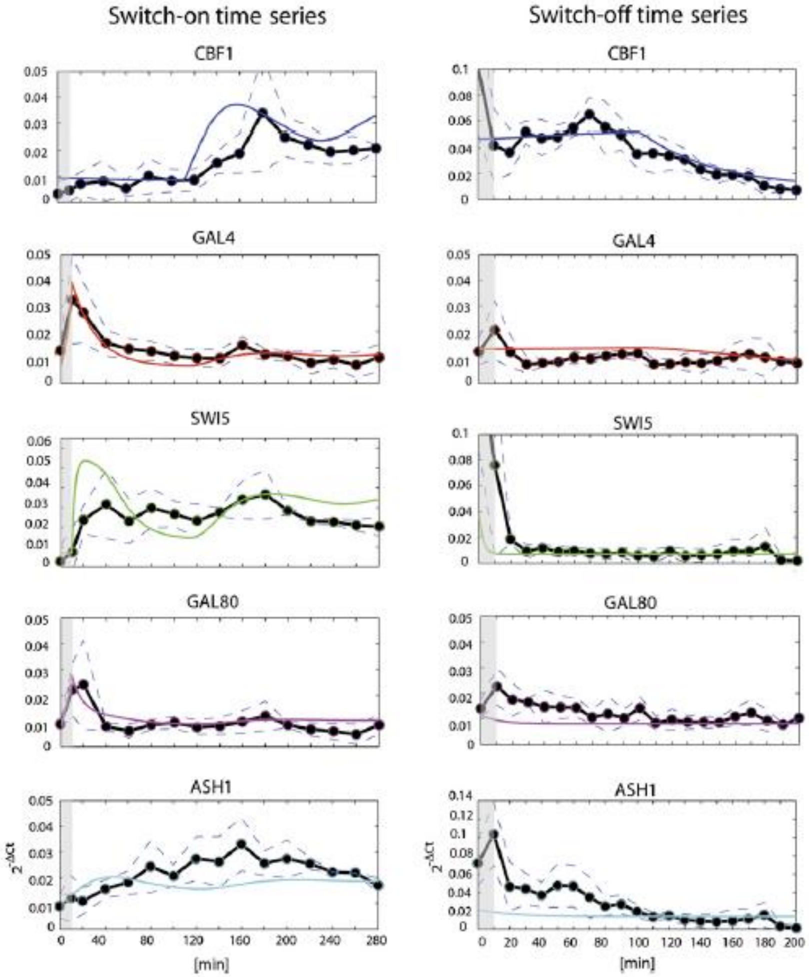


Cantone *et al.* (2009), *Cell*, 137(1):172-81

IRMA: synthetic network in yeast

- IRMA proposed as a benchmark for modeling and identification approaches
- IRMA dynamics measured over time in galactose (switch-on) and glucose (switch-off)

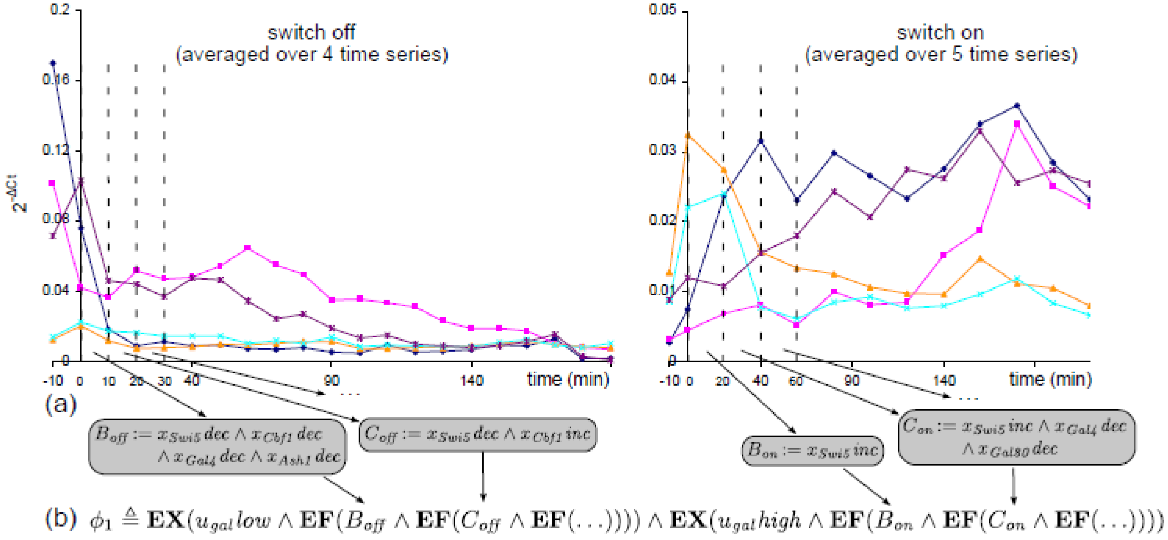
  Quantitative RT-PCR
- **Question**: are measured dynamics consistent with constructed network structure?



Cantone *et al.* (2009), *Cell*, 137(1):172-81

Test of consistency structure-dynamics

- Development of (unparametrized) PL model representing network structure
- Approach to test consistency between network structure and data based on automated parameter constraint search:
  - Generate temporal logic formulae encoding observed network dynamics



$B_{\mathit{off}} := x_{\mathit{Swi5}}\,\mathit{dec} \wedge x_{\mathit{Cbf1}}\,\mathit{dec} \wedge x_{\mathit{Gal4}}\,\mathit{dec} \wedge x_{\mathit{Ash1}}\,\mathit{dec}$

$C_{\mathit{off}} := x_{\mathit{Swi5}}\,\mathit{dec} \wedge x_{\mathit{Cbf1}}\,\mathit{inc}$

$B_{on} := x_{\mathit{Swi5}}\,\mathit{inc}$

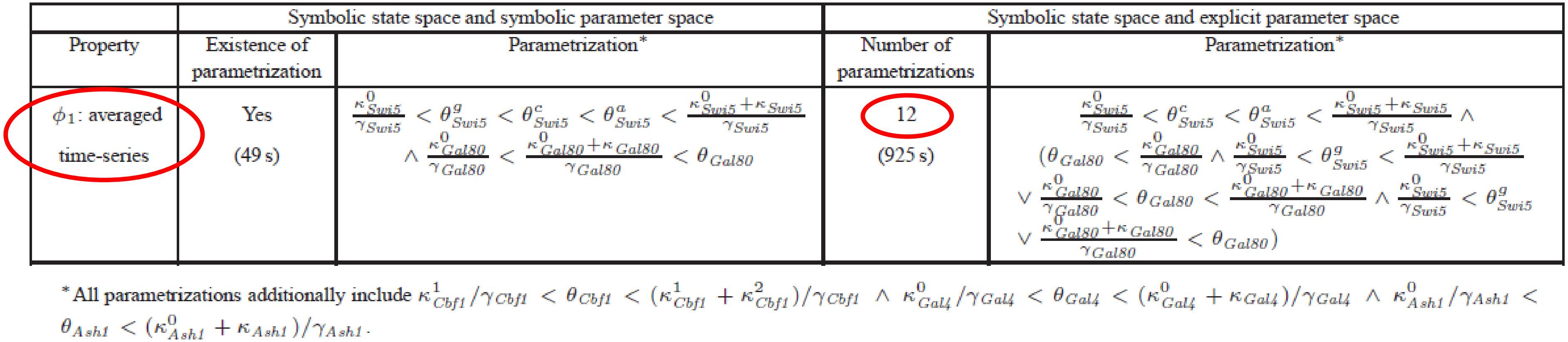
$C_{on} := x_{\mathit{Swi5}}\,\mathit{inc} \wedge x_{\mathit{Gal4}}\,\mathit{dec} \wedge x_{\mathit{Gal80}}\,\mathit{dec}$

(b) $\phi_1 \triangleq \mathbf{EX}(u_{gal}\,low \wedge \mathbf{EF}(B_{\mathit{off}} \wedge \mathbf{EF}(C_{\mathit{off}} \wedge \mathbf{EF}(\ldots)))) \wedge \mathbf{EX}(u_{gal}\,high \wedge \mathbf{EF}(B_{on} \wedge \mathbf{EF}(C_{on} \wedge \mathbf{EF}(\ldots))))$

Batt *et al.* (2010), *Bioinformatics*, 26(18):i603-10

Test of consistency structure-dynamics

- Development of (unparametrized) PL model representing network structure
- Approach to test consistency between network structure and data based on automated parameter constraint search:
  - Generate temporal logic formulae encoding observed network dynamics
  - Test if there are any parametrizations of PL model satisfy temporal logic formulae



	Symbolic state space and symbolic parameter space		Symbolic state space and explicit parameter space	
Property	Existence of parametrization	Parametrization*	Number of parametrizations	Parametrization*
ϕ_1: averaged time-series	Yes (49 s)	$\frac{\kappa^0_{Swi5}}{\gamma_{Swi5}} < \theta^g_{Swi5} < \theta^c_{Swi5} < \theta^a_{Swi5} < \frac{\kappa^0_{Swi5}+\kappa_{Swi5}}{\gamma_{Swi5}} \wedge \frac{\kappa^0_{Gal80}}{\gamma_{Gal80}} < \frac{\kappa^0_{Gal80}+\kappa_{Gal80}}{\gamma_{Gal80}} < \theta_{Gal80}$	12 (925 s)	$\frac{\kappa^0_{Swi5}}{\gamma_{Swi5}} < \theta^c_{Swi5} < \theta^a_{Swi5} < \frac{\kappa^0_{Swi5}+\kappa_{Swi5}}{\gamma_{Swi5}} \wedge (\theta_{Gal80} < \frac{\kappa^0_{Gal80}}{\gamma_{Gal80}} \wedge \frac{\kappa^0_{Swi5}}{\gamma_{Swi5}} < \theta^g_{Swi5} < \frac{\kappa^0_{Swi5}+\kappa_{Swi5}}{\gamma_{Swi5}} \vee \frac{\kappa^0_{Gal80}}{\gamma_{Gal80}} < \theta_{Gal80} < \frac{\kappa^0_{Gal80}+\kappa_{Gal80}}{\gamma_{Gal80}} \wedge \frac{\kappa^0_{Swi5}}{\gamma_{Swi5}} < \theta^g_{Swi5} \vee \frac{\kappa^0_{Gal80}+\kappa_{Gal80}}{\gamma_{Gal80}} < \theta_{Gal80})$

* All parametrizations additionally include $\kappa^1_{Cbf1}/\gamma_{Cbf1} < \theta_{Cbf1} < (\kappa^1_{Cbf1} + \kappa^2_{Cbf1})/\gamma_{Cbf1} \wedge \kappa^0_{Gal4}/\gamma_{Gal4} < \theta_{Gal4} < (\kappa^0_{Gal4} + \kappa_{Gal4})/\gamma_{Gal4} \wedge \kappa^0_{Ash1}/\gamma_{Ash1} < \theta_{Ash1} < (\kappa^0_{Ash1} + \kappa_{Ash1})/\gamma_{Ash1}$.

Test of consistency structure-dynamics

- Development of (unparametrized) PL model representing network structure
- Approach to test consistency between network structure and data based on automated parameter constraint search:
  - Generate temporal logic formulae encoding observed network dynamics
  - Test if there are any parametrizations of PL model satisfy temporal logic formulae
  - Analyze parametrizations for biological plausibility

« Activation threshold of CBF1 by Swi5 higher than activation threshold of ASH1 »: confirmed by independent experimental data

Batt *et al.* (2010), *Bioinformatics*, 26(18):i603-10

Test of consistency structure-dynamics

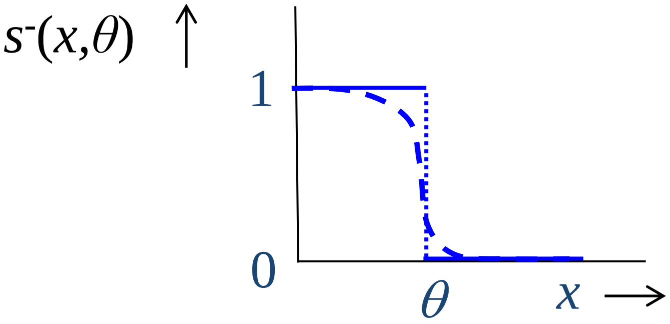
- Development of (unparametrized) PL model representing network structure
- Approach to test consistency between network structure and data based on automated parameter constraint search:
  - Generate temporal logic formulae encoding observed network dynamics
  - Test if there are any parametrizations of PL model satisfy temporal logic formulae
  - Analyze parametrizations for biological plausibility
- Automated approach for testing consistency based on model-checking techniques

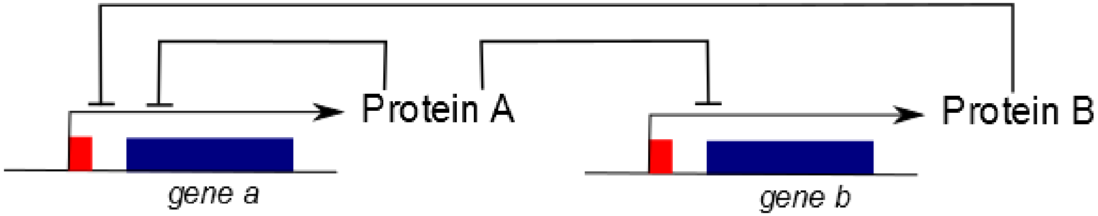
  Symbolic encoding of model, dynamics and properties to make problem feasible

PL differential equation models

- ODE models approximated by means of **step functions** to describe regulatory interactions

$$\dot{x}_a = \kappa_a \, s^-(x_a, \theta_{a2}) \, s^-(x_b, \theta_b) - \gamma_a \, x_a$$
$$\dot{x}_b = \kappa_b \, s^-(x_a, \theta_{a1}) - \gamma_b \, x_b$$





x : protein concentration
θ : threshold concentration
κ , γ : rate constants

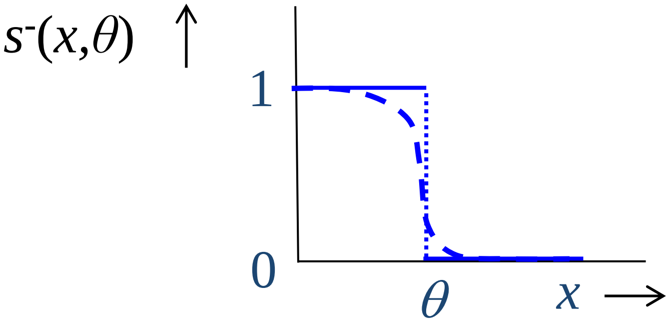
- Expressions of step functions account for combinatorial control of gene expression (AND, OR, NOR, …)

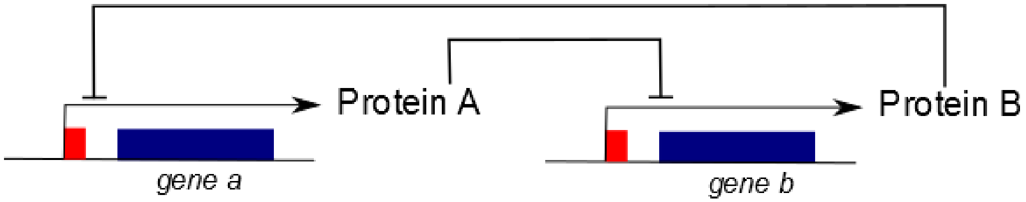
PL differential equation models

- ODE models approximated by means of **step functions** to describe regulatory interactions

$$\dot{x}_a = \kappa_a\, s^-(x_b, \theta_b) - \gamma_a\, x_a$$

$$\dot{x}_b = \kappa_b\, s^-(x_a, \theta_a) - \gamma_b\, x_b$$





x : protein concentration

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κ , γ : rate constants

Boolean models

- **Boolean models** are discrete models of dynamics of gene regulatory networks

  Thomas and d'Ari (1990), *Biological Feedback*, CRC Press

  Kauffman (1993), *The Origins of Order*, Oxford University Press

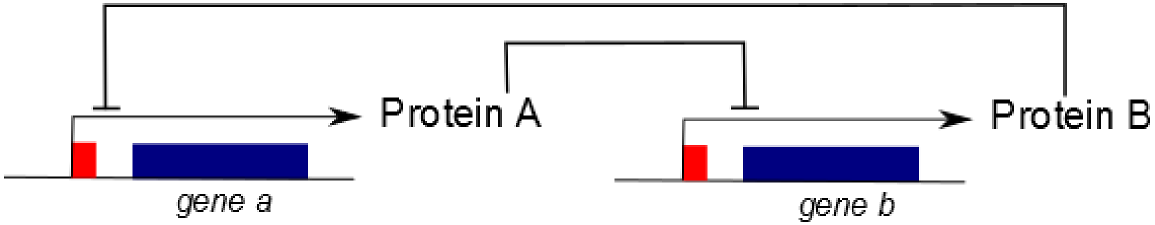
  Wang et al. (2012), *Phys. Biol.,* 9(5):055001

- Boolean variables discretize state of gene regulatory network

$$X_a \in \{0, 1\}, X_b \in \{0, 1\}$$

$$X_a = (x_a > \theta_a), X_b = (x_b > \theta_b)$$

$$X_a^{\,t}, X_b^{\,t}, t = 0, 1, 2, \ldots$$



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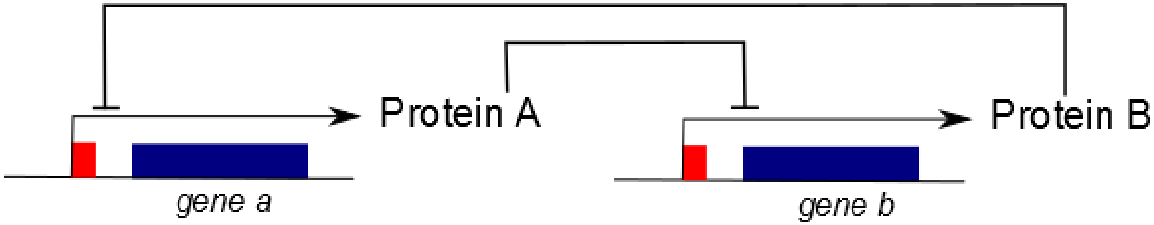
- Boolean variables discretize state of gene regulatory network
- Boolean functions represent control of gene expression

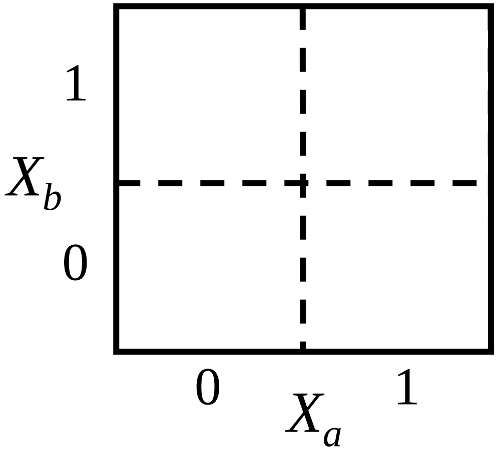
$$X_a^{t+1} = \text{NOT } X_b^t$$

$$X_b^{t+1} = \text{NOT } X_a^t$$



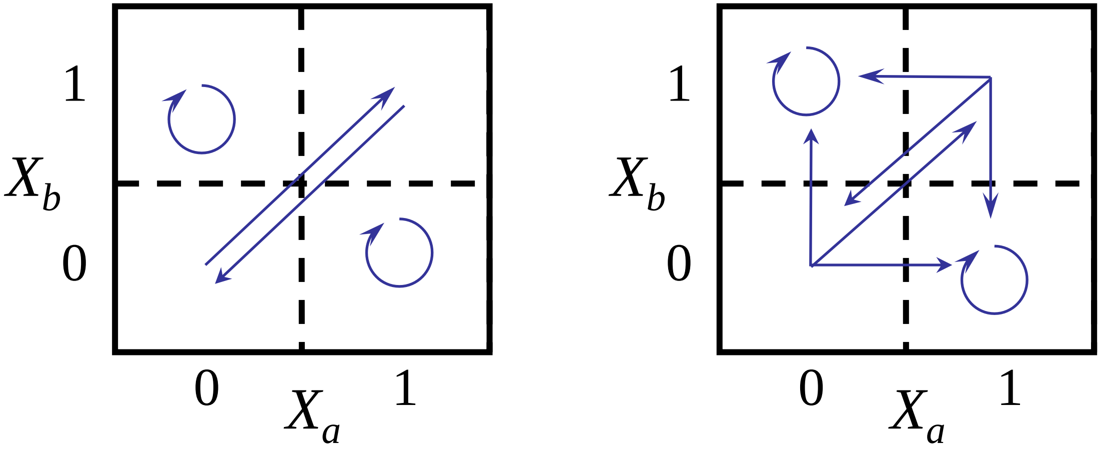
Analysis of Boolean models

- Boolean models can be analyzed in discrete state space



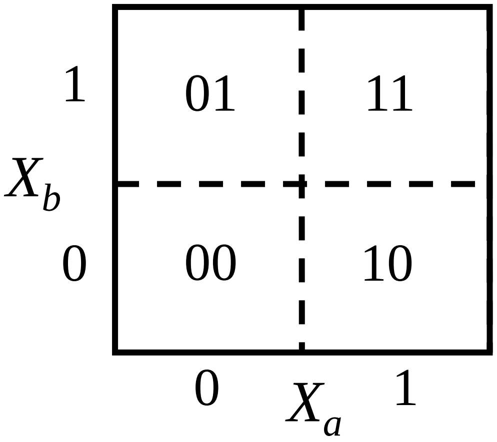
$$X_a^{t+1} = \text{NOT } X_b^{t}$$
$$X_b^{t+1} = \text{NOT } X_a^{t}$$

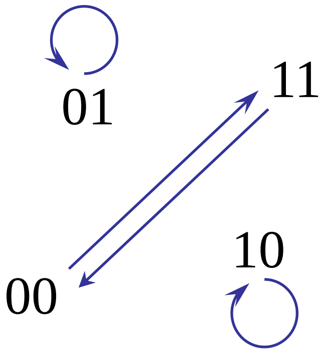
- **Synchrone** and **asynchrone** dynamics



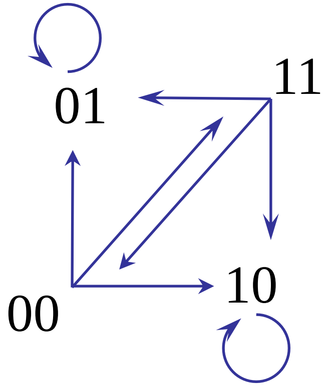
Analysis of Boolean models

- Dynamics of Boolean models can also be represented in **state transition graph**
  - Different graphs for synchrone and asynchrone dynamics
  - Attractors (states or cycles)



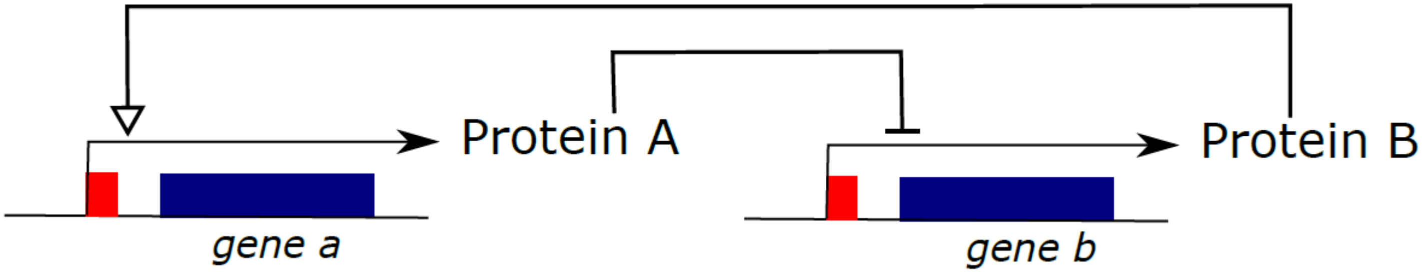


synchrone



asynchrone

Analysis of Boolean models



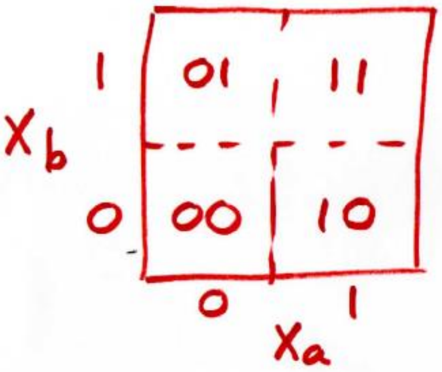
- Question: write out Boolean model for repressilator
- Question: construct state transition graph with synchronic and asynchronic

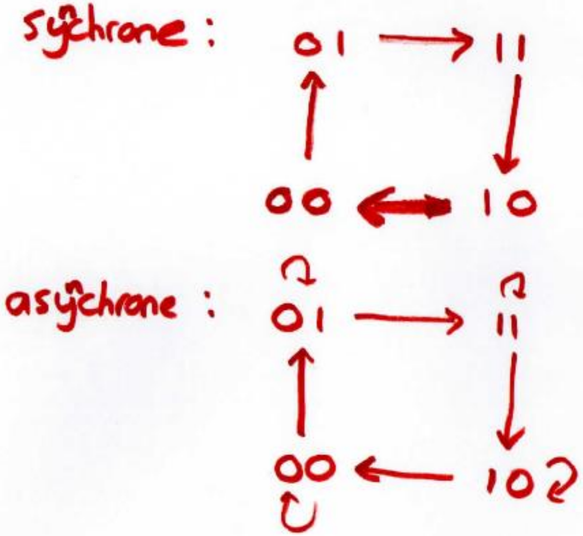
Analysis of Boolean models

- Question: write out Boolean model for repressilator
- Question: construct state transition graph with synchronic and asynchronic

$$X_a^{t+1} = X_b^{t}$$

$$X_b^{t+1} = \text{NOT } X_a^{t}$$





Generalized logical models

- **Generalized logical models** are discrete models of dynamics of gene regulatory networks

  Thomas and d'Ari (1990), *Biological Feedback*, CRC Press

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- Logical variables discretize state of gene regulatory network

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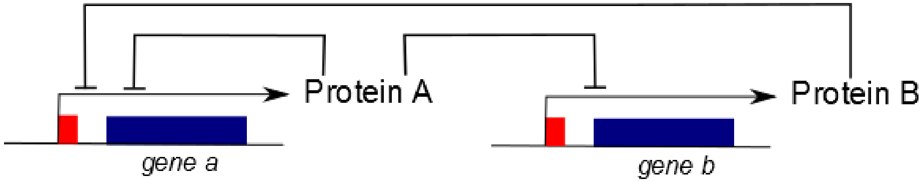

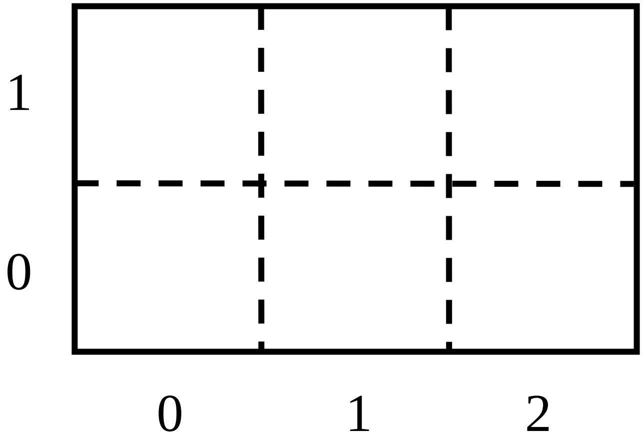

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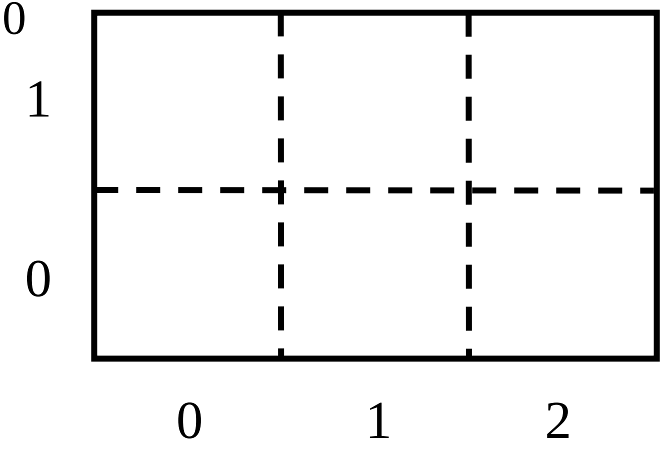
- Logical variables discretize state of gene regulatory network
- Boolean functions represent control of gene expression

$$X_a^{t+1} = 2, \text{ if } (X_a^t = 0 \text{ OR } X_a^t = 1) \text{ AND } X_b^t = 0$$

$$X_a^{t+1} = 0, \text{ if } X_a^t = 2 \text{ OR } X_b^t = 1$$

$$X_b^{t+1} = 1, \text{ if } X_a^t = 0$$

$$X_b^{t+1} = 0, \text{ if } X_a^t = 1 \text{ OR } X_a^t = 2$$



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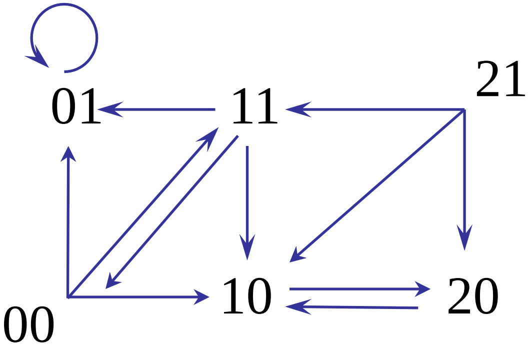

asynchrone

Generalized logical models

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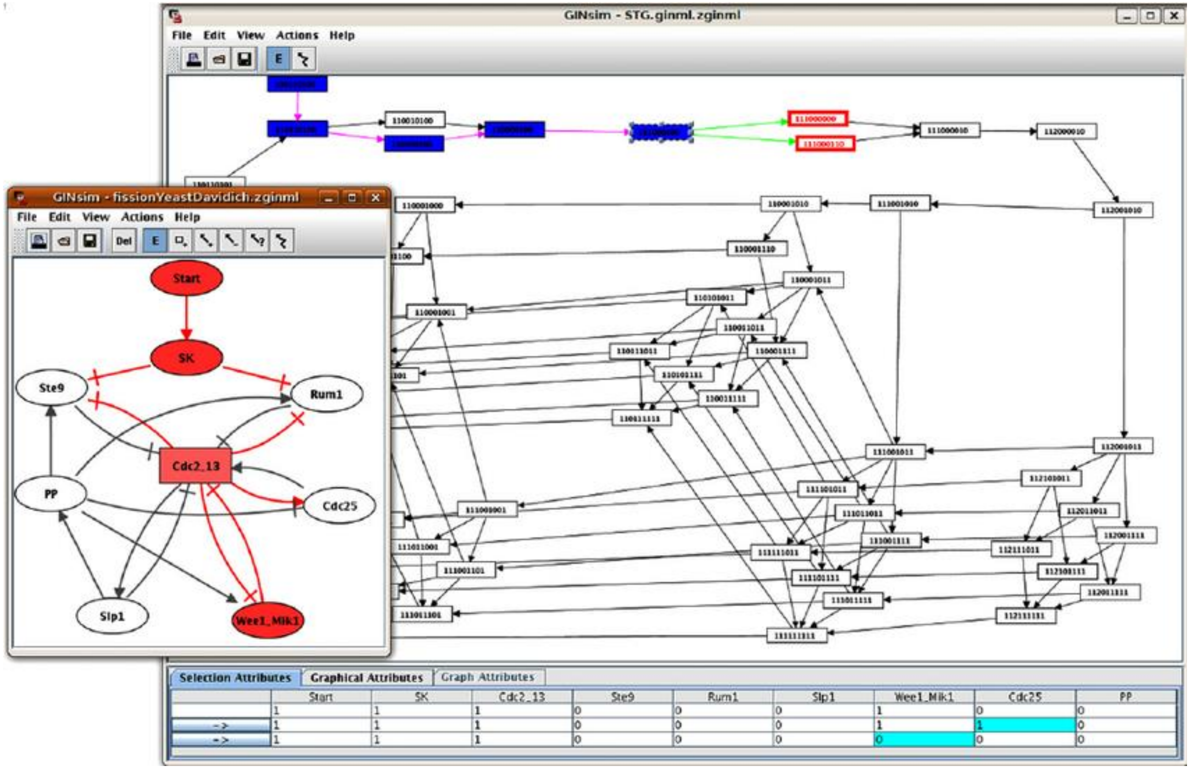
- Logical variables discretize state of gene regulatory network
- Boolean functions represent control of gene expression
- Dynamics can be represented by state transition graph
- Close correspondence between discrete abstractions of PLDE models and generalized logical models

GinSIM

- **GinSIM**: computer tool for logical modeling of regulatory networks

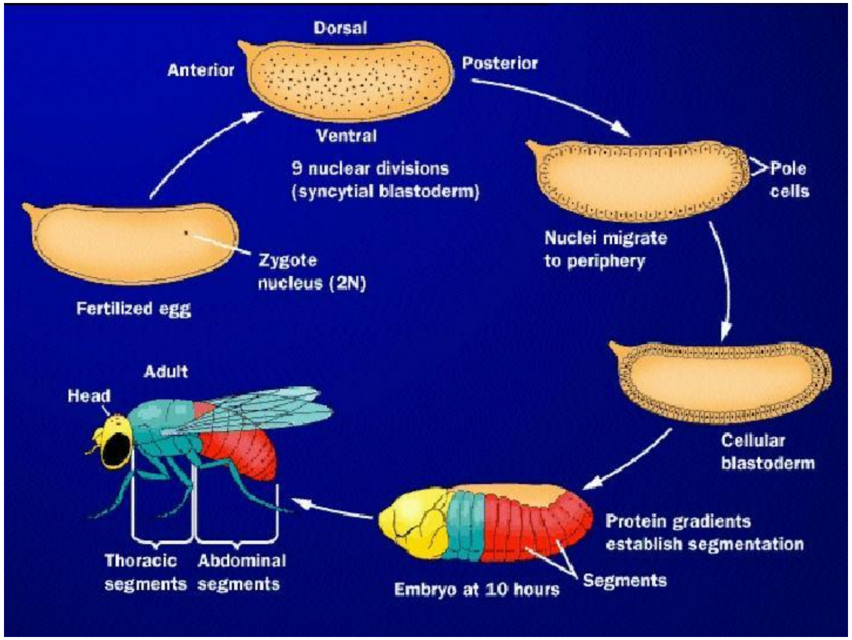


	Start	SK	Cdc2_13	Ste9	Rum1	Slp1	Wee1_Mik1	Cdc25	PP
	1	1	1	0	0	0	1	0	0
->	1	1	1	0	0	0	1	1	0
->	1	1	1	0	0	0	0	0	0

Chaouiya *et al.* (2012), *Methods Mol. Biol.*, 804:463-79

Development of *Drosophila* embryon

- Development of *Drosophila melanogaster* (fruit fly)



Purves *et al.* (1998), *Life: The Science of Biology*, Sinauer

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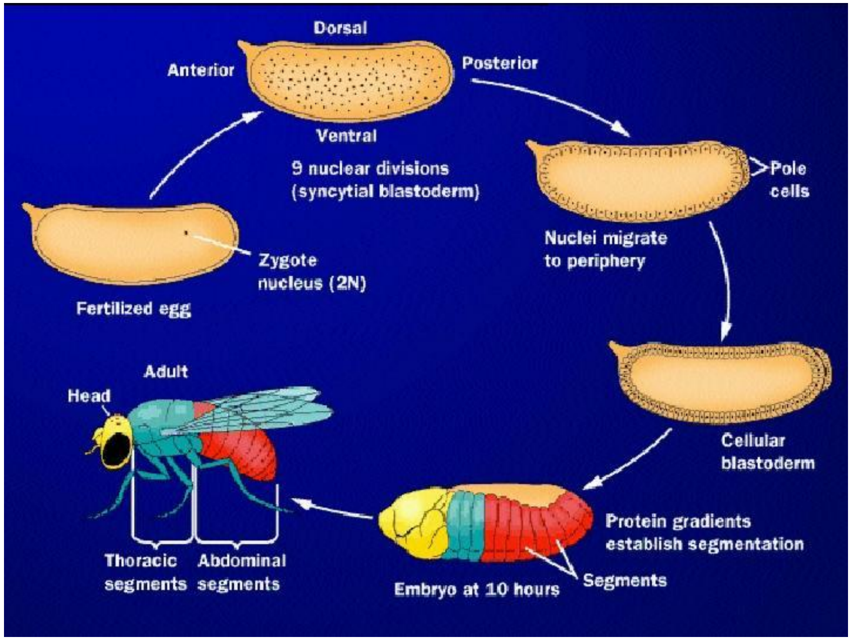
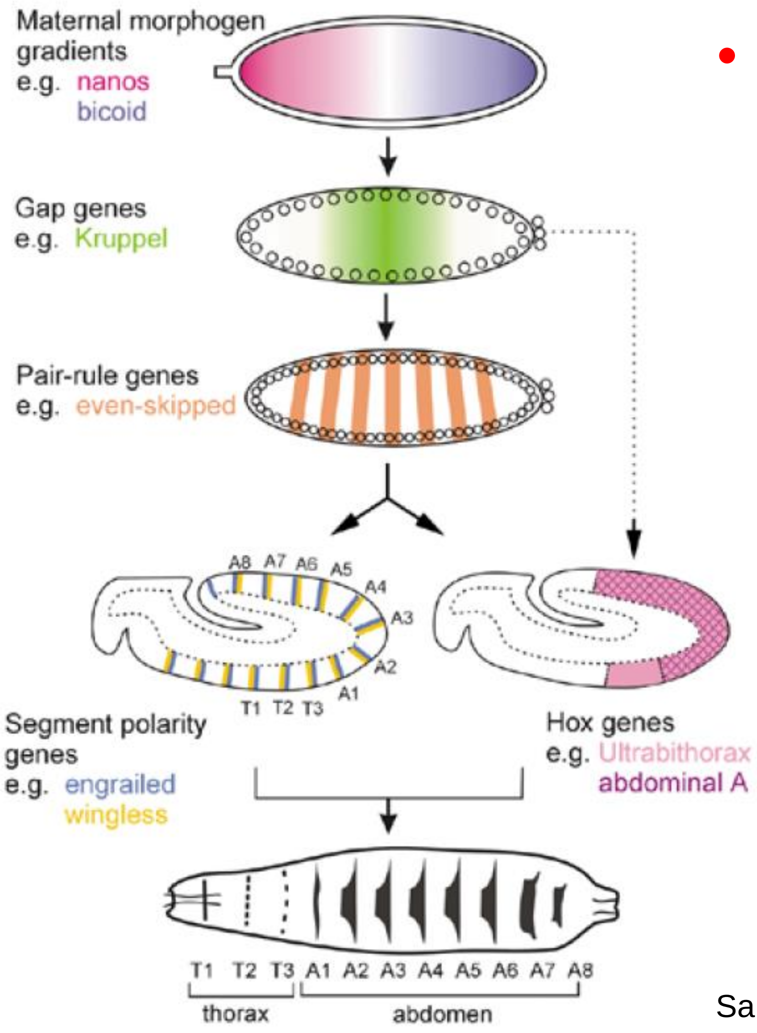


Purves *et al.* (1998), *Life: The Science of Biology*, Sinauer

Tomer *et al.* (2012), *Nat. Methods*, 9(7):755–63

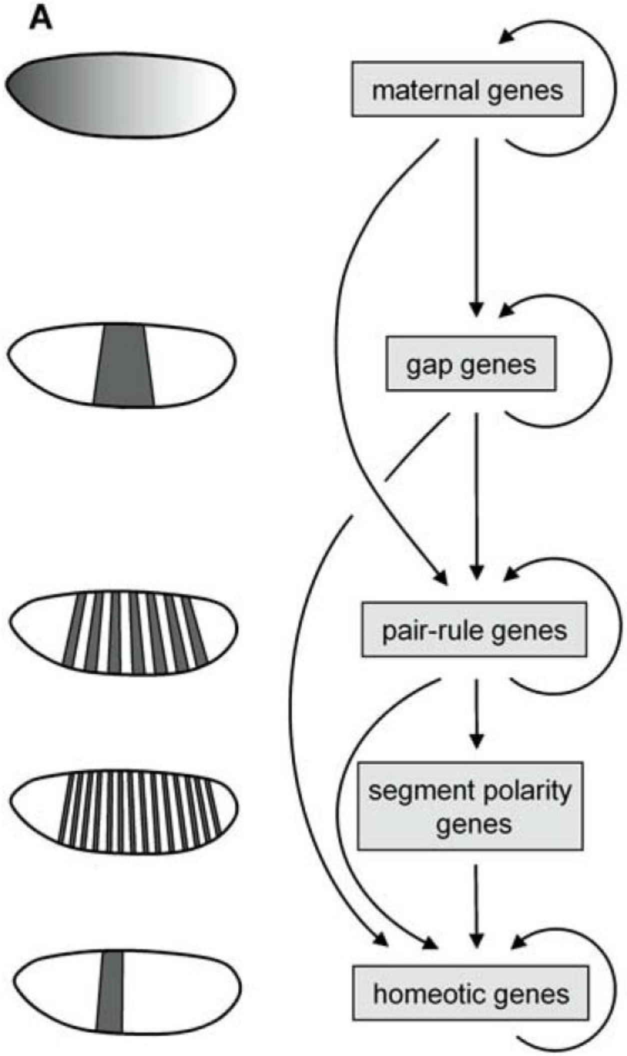
Development of *Drosophila* embryon



- Spatiotemporal gene expression patterns during early development of *Drosophila* (fruit fly)

Sanson (2001), *EMBO Rep.*, 2(12):1083–8

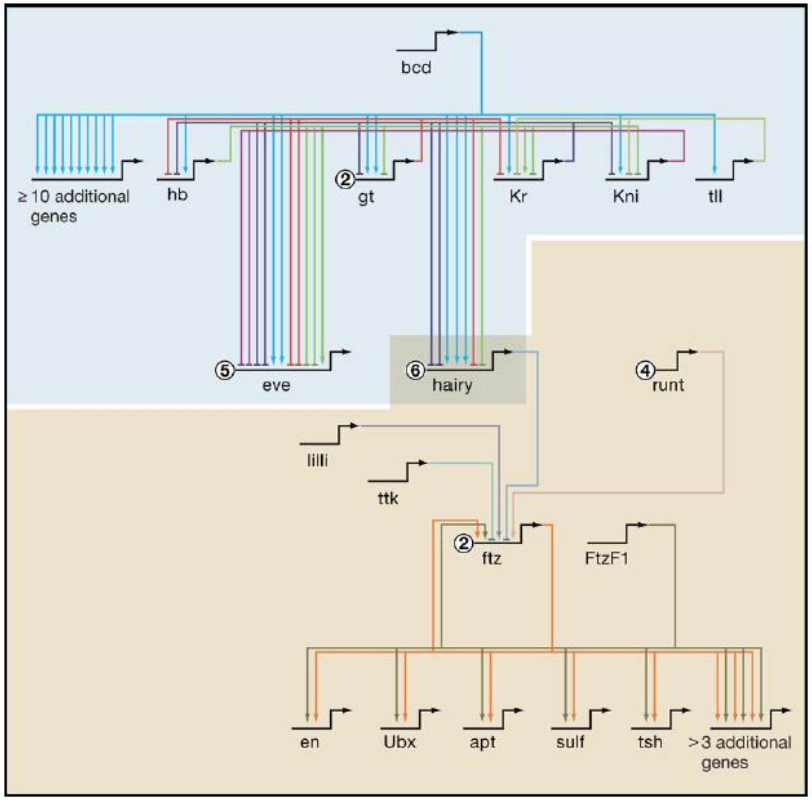
Development of *Drosophila* embryon



- Spatiotemporal gene expression patterns during early development of *Drosophila* (fruit fly)
- Gene classes and their interactions responsible for establishment of gene expression patterns

Schroeder *et al.* (2004), *PLoS Biol.*, 4(2):e271

Development of *Drosophila* embryon

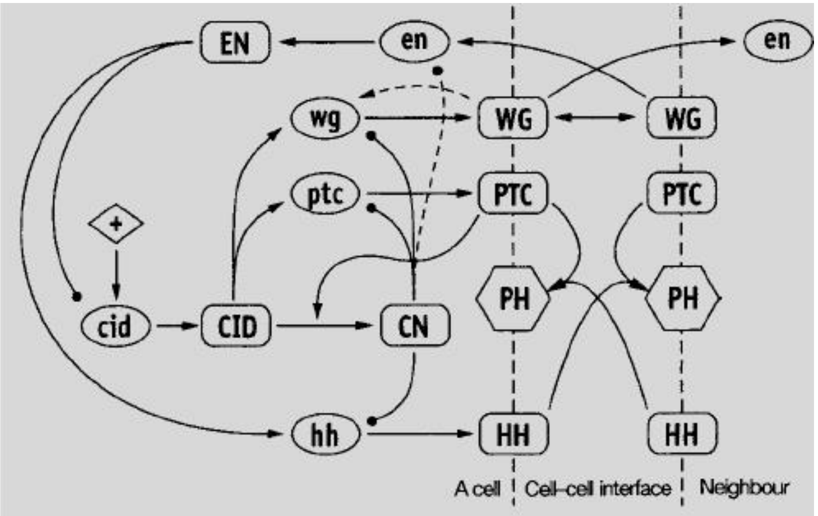


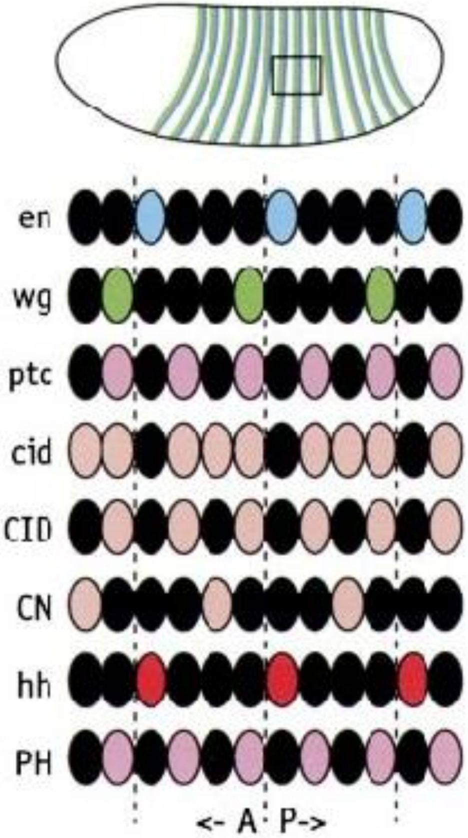
Carroll (2008), *Cell*, 134(1):25-36

- Spatiotemporal gene expression patterns during early development of *Drosophila* (fruit fly)
- Gene classes and their interactions responsible for establishment of gene expression patterns
- Complex gene regulatory networks

Model of *Drosophila* segmentation

- Model of network of **segment polarity** genes in early development of *Drosophila*

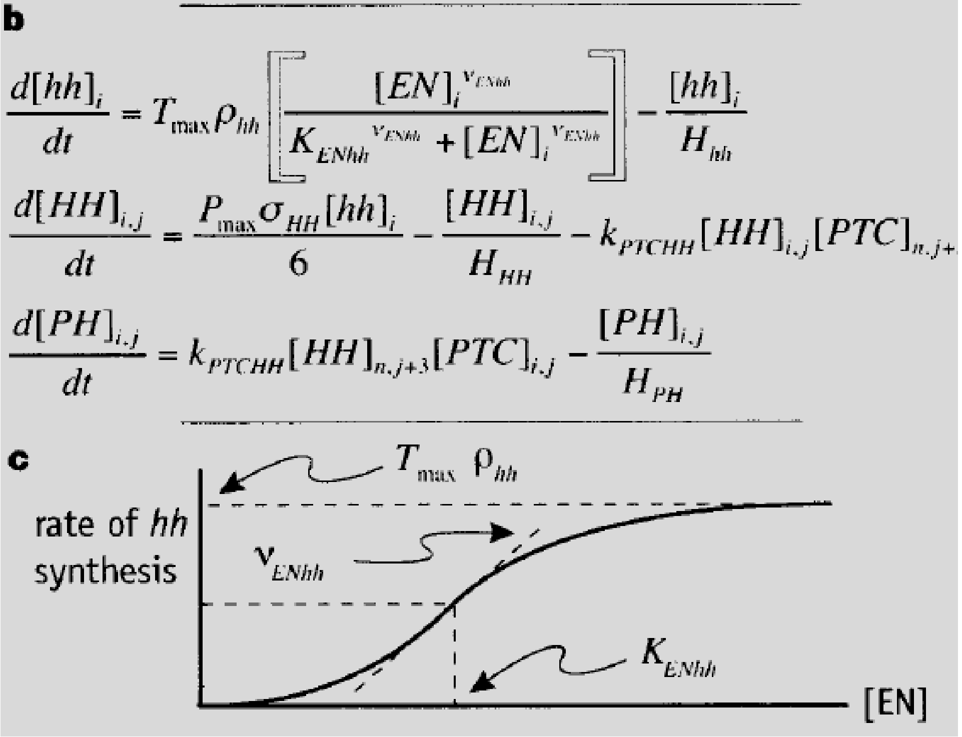




von Dassow *et al.* (2000), *Nature*, 406(6792): 188-92

Model of *Drosophila* segmentation

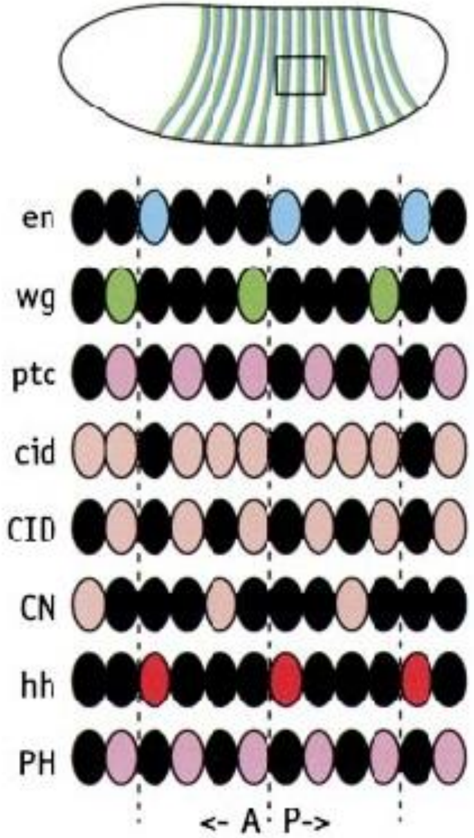
- Model of network of **segment polarity** genes in early development of *Drosophila*
    - 13 ODEs per cell and 48 parameters



$$\frac{d[hh]_i}{dt} = T_{\max}\rho_{hh}\left[\frac{[EN]_i^{\nu_{ENhh}}}{K_{ENhh}^{\nu_{ENhh}} + [EN]_i^{\nu_{ENhh}}}\right] - \frac{[hh]_i}{H_{hh}}$$

$$\frac{d[HH]_{i,j}}{dt} = \frac{P_{\max}\sigma_{HH}[hh]_i}{6} - \frac{[HH]_{i,j}}{H_{HH}} - k_{PTCHH}[HH]_{i,j}[PTC]_{n,j+}$$

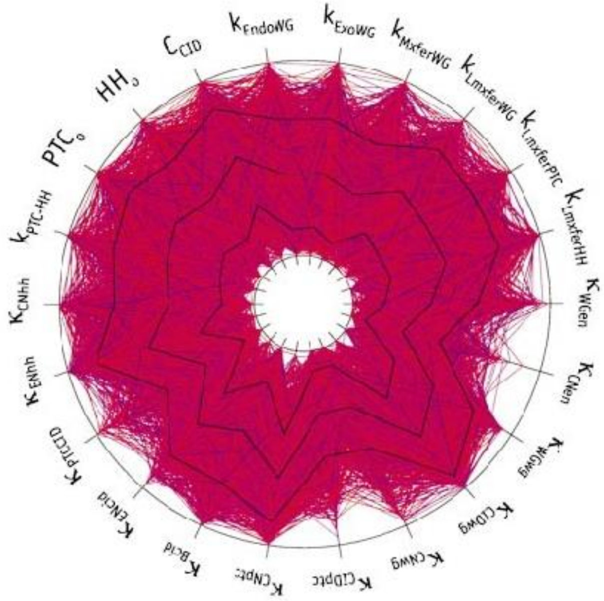
$$\frac{d[PH]_{i,j}}{dt} = k_{PTCHH}[HH]_{n,j+3}[PTC]_{i,j} - \frac{[PH]_{i,j}}{H_{PH}}$$

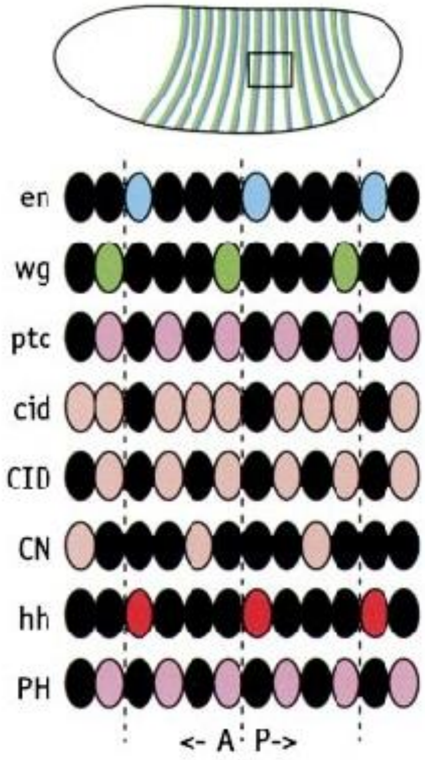


von Dassow *et al.* (2000), *Nature*, 406(6792): 188-92

Robustness of gene expression patterns

- Spatial expression pattern of segment polarity genes **robustly reproduced** over large ranges of parameter values
    - 0.5% of sampled parameter combinations leads to solution compatible with data





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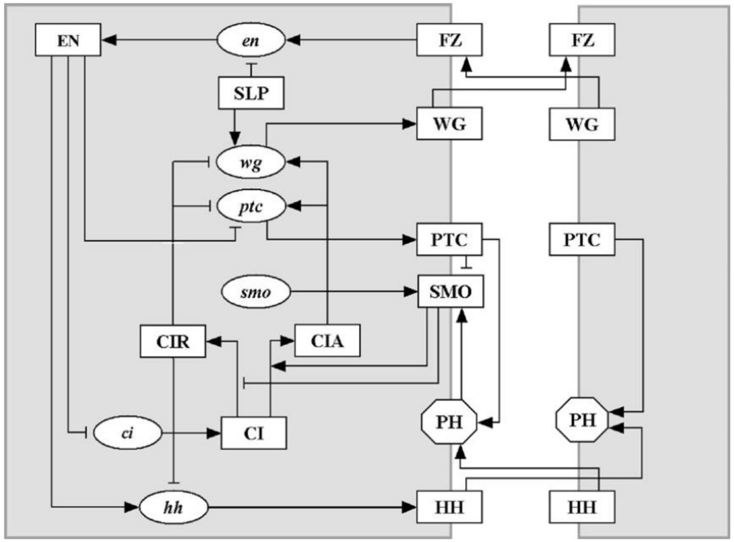
Logical model of *Drosophila* segmentation

- **Logical model** of segment polarity network: variables take values 0/1 and Boolean functions to update variables



Albert and Othmer (2003), *J. Theor. Biol.*, 223(1):1-18

hh_i

HH_i

ptc_i

PTC_i

PH_i

$$hh_i^{t+1} = EN_i^t \text{ and not } CIR_i^t$$

$$HH_i^{t+1} = hh_i^t$$

$$ptc_i^t = CIA_i^{t+1} \text{ and not } EN_i^t \text{ and not } CIR_i^t$$

$$PTC_i^{t+1} = ptc_i^t \text{ or } (PTC_i^t \text{ and not } HH_{i-1}^t \text{ and not } HH_{i+1}^t)$$

$$PH_i^t = PTC_i^t \text{ and } (HH_{i-1}^t \text{ or } HH_{i+1}^t)$$

Logical model of *Drosophila* segmentation

- **Logical model** of segment polarity network: variables take values 0/1 and Boolean functions to update variables
- Logical models are based on topology of network only (no parametrization), but are capable of reproducing experimental data: **robustness**

Observed initial state (before stage 8)

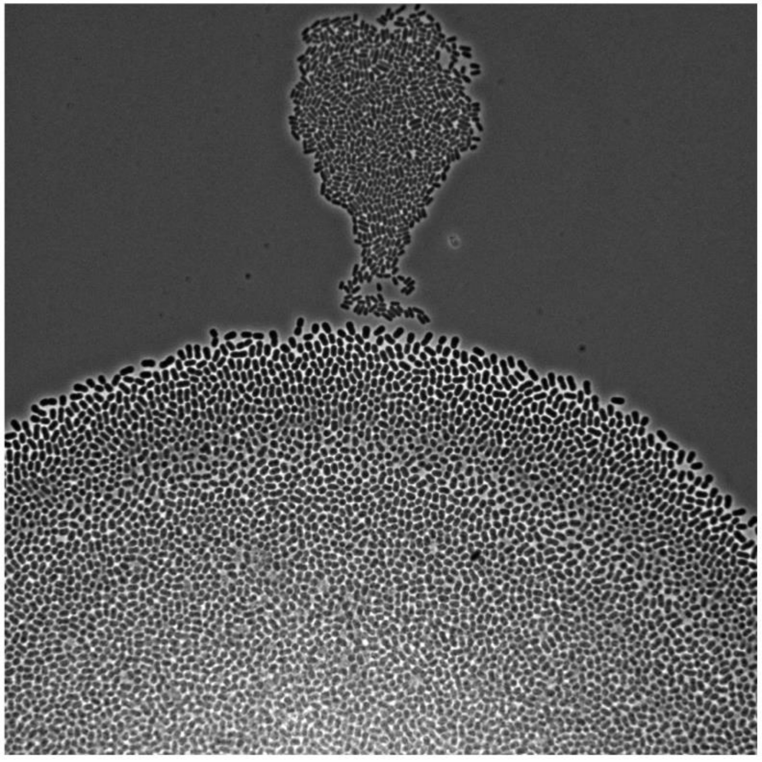
Predicted steady state state (during stages 9-11)

Albert and Othmer (2003), *J. Theor. Biol.*, 223(1):1-18

Conclusions

- Modeling of genetic regulatory networks in bacteria often hampered by lack of information on parameter values
- Use of coarse-grained discrete or discretized models that provide reasonable approximation of dynamics
- Mathematical methods and computer tools for analysis of qualitative dynamics of discrete models
- Use of discrete models may gain insight into functioning of large and complex networks
- Discrete, coarse-grained models provide first idea of qualitative dynamics that may guide quantitative modeling

Thanks!



team.inria.fr/microcosme