

# Qualitative Modeling and Simulation of Genetic Regulatory Networks

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<http://ibis.inrialpes.fr>

# INRIA Grenoble - Rhône-Alpes and IBIS



- ❖ IBIS: systems biology group of INRIA and Joseph Fourier University/CNRS
  - Analysis of bacterial regulatory networks by means of models and experiments
  - Involves molecular biologists, mathematicians, physicists, computer scientists, ...

# Overview

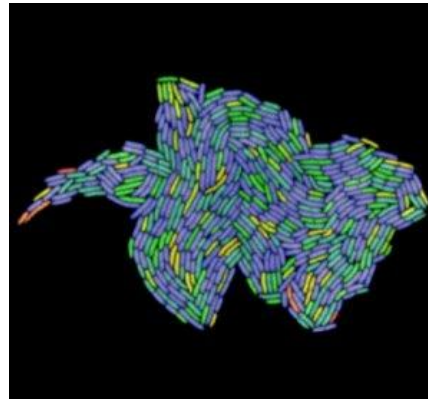
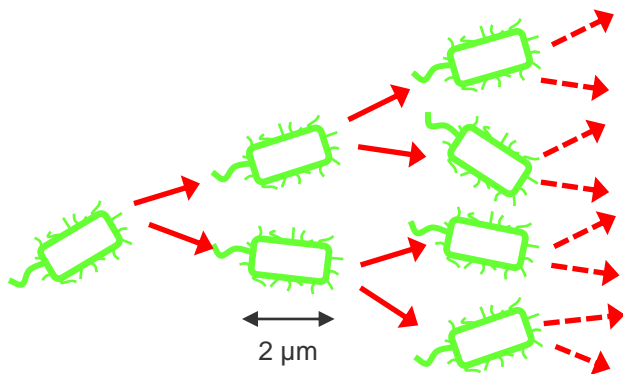
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1. Genetic regulatory networks in bacteria
2. Qualitative simulation of genetic regulatory networks using piecewise-linear models
3. Qualitative simulation of carbon starvation response in *Escherichia coli*: model predictions and validation
4. Perspectives: towards quantitative models

# Bacterial growth and adaptation

- ❖ Bacteria are geared towards growth and division

*E. coli* cells have doubling times up to 20 min



Stewart et al. (2005), *PLoS Biol.*, 3(2): e45

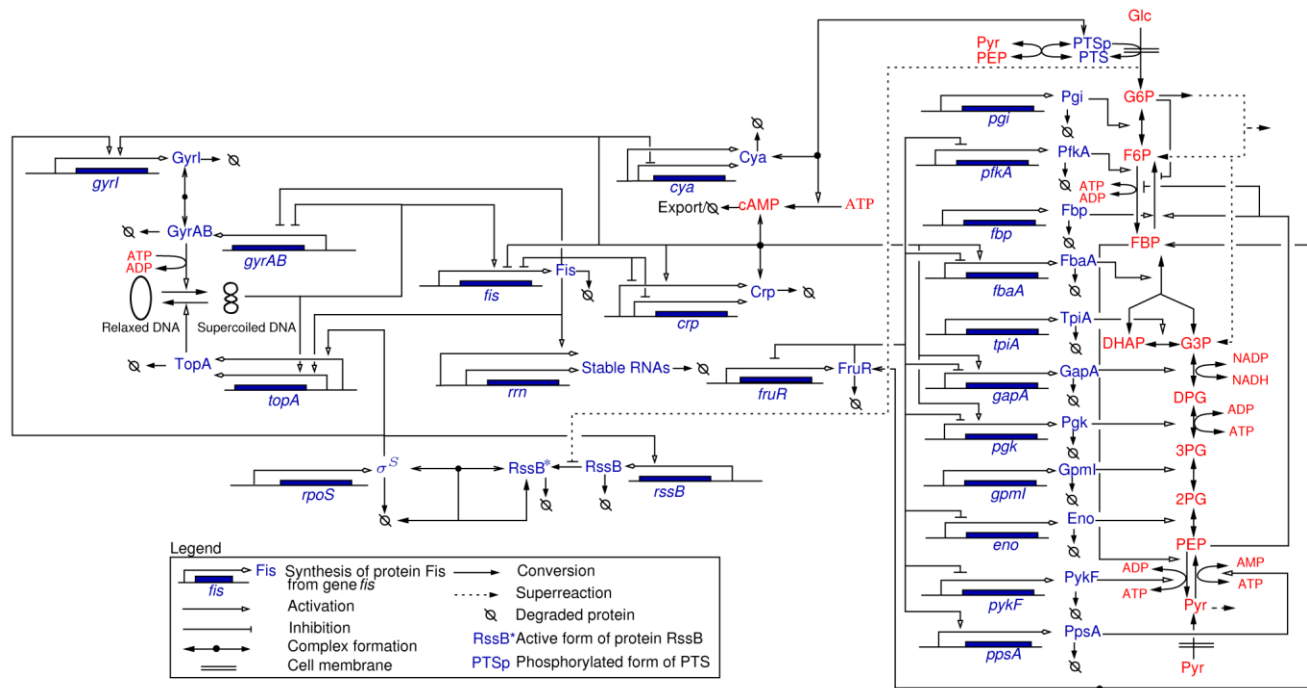
- ❖ Changes in environment may cause adaptation of growth rate, and more generally, physiology of bacterial cell

Nutrient starvation, heat shock, osmotic stress, high population density, ...

# Molecular basis of growth adaptation

- ❖ Adaptation of growth rate and other stress responses involves complex **regulatory networks**

Network of biochemical reactions underlying carbon assimilation in *E. coli*

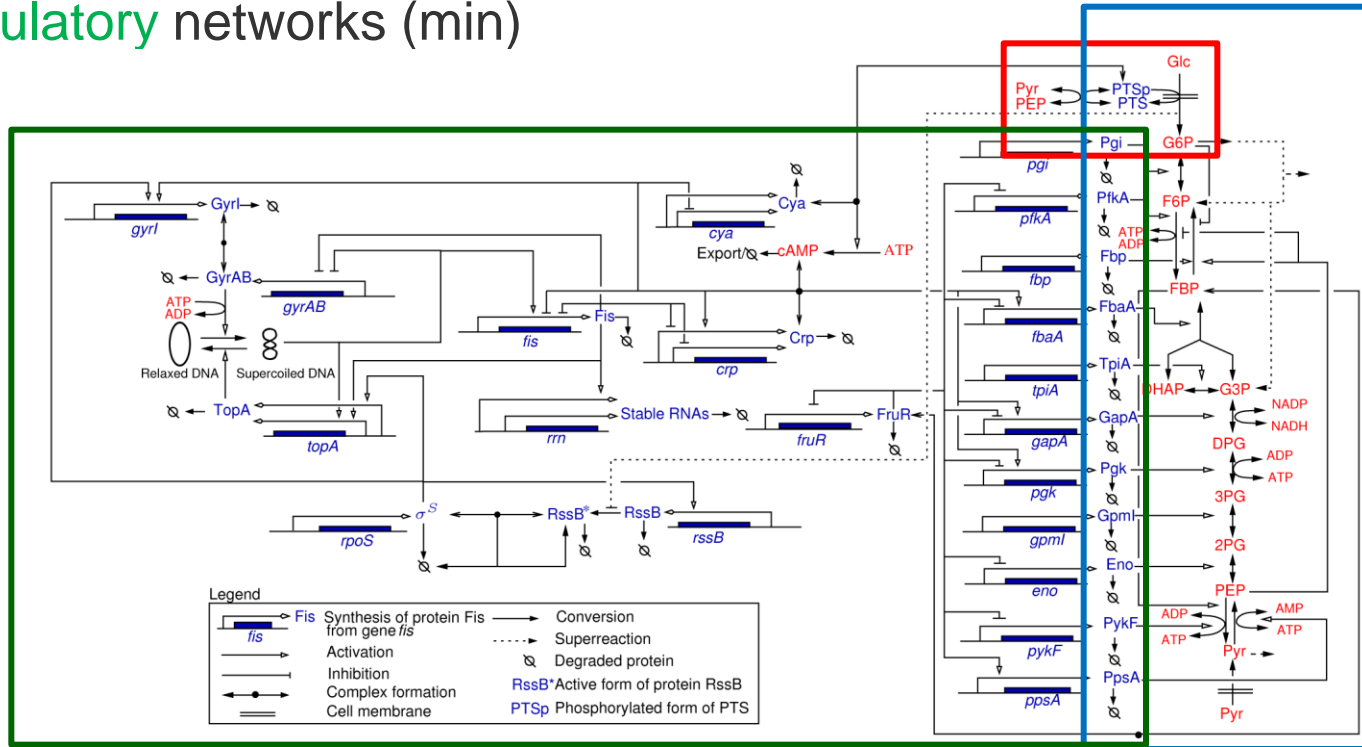


Baldazzi et al. (2010), *PLoS Comput. Biol.*, 6(6):e1000812

# Different time-scales, different networks

- Variety of biochemical reactions, occurring on different time-scales, define different types of networks

Signal transduction networks (ms), metabolic networks (s), gene regulatory networks (min)



# Gene regulatory networks

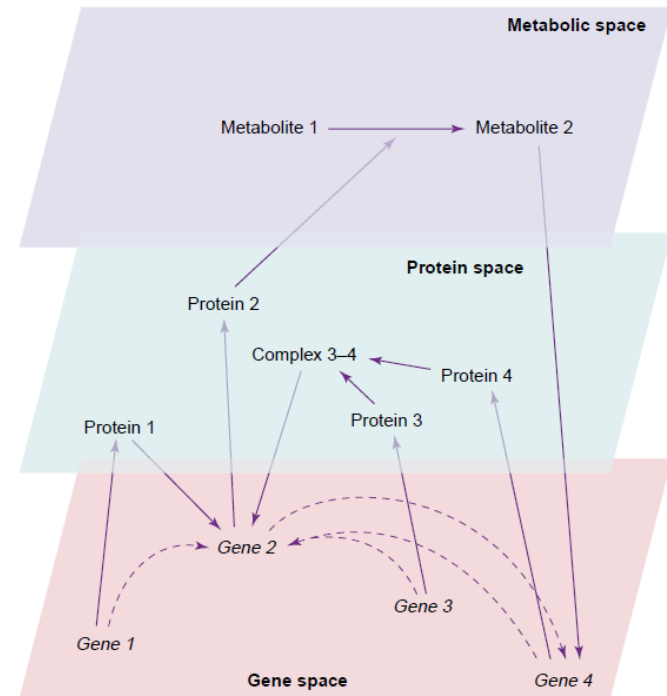
- ❖ **Gene regulatory networks** control long-term adaptation of bacterial cell to external perturbations

Genes, gene products (RNAs, proteins), and the regulatory effect of the latter on the expression of other genes

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

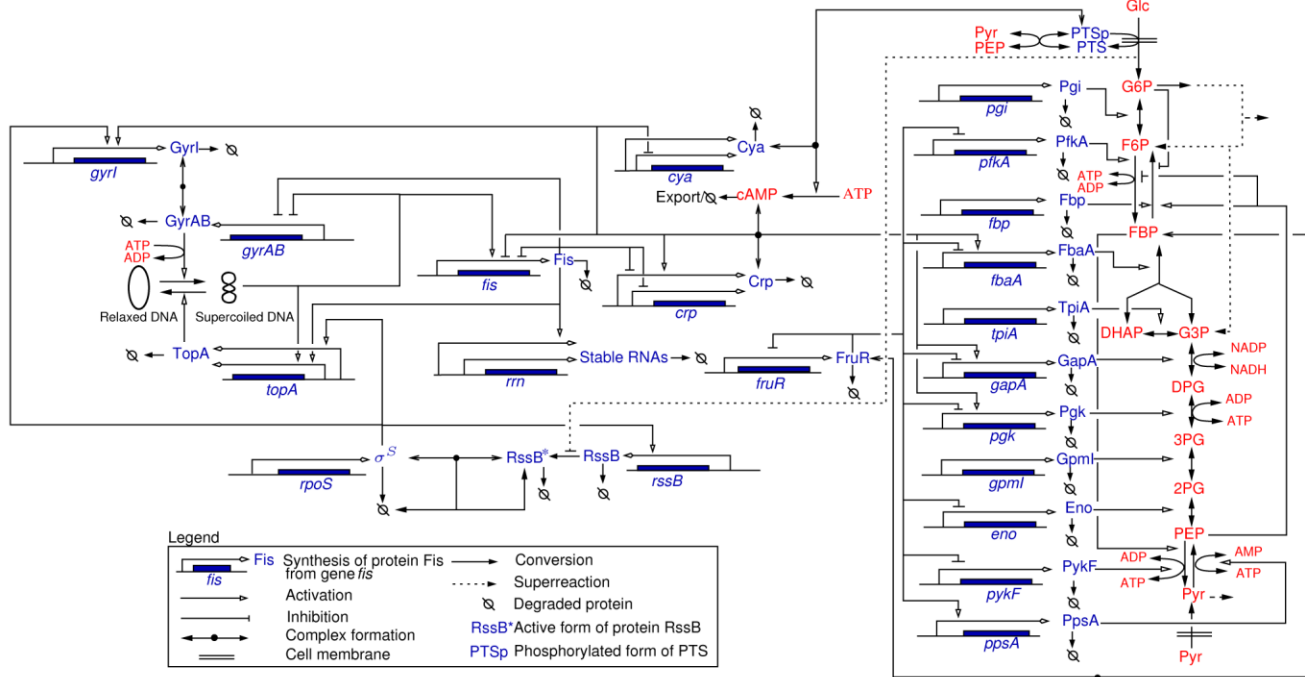
- ❖ Gene regulatory networks cannot be reduced to **direct** interactions (transcription regulation), but also include **indirect** interactions (mediated by metabolism)

Brazhnik et al. (2002), *Trends Biotechnol.*, 20(11):467-72





# Structure of gene regulatory networks



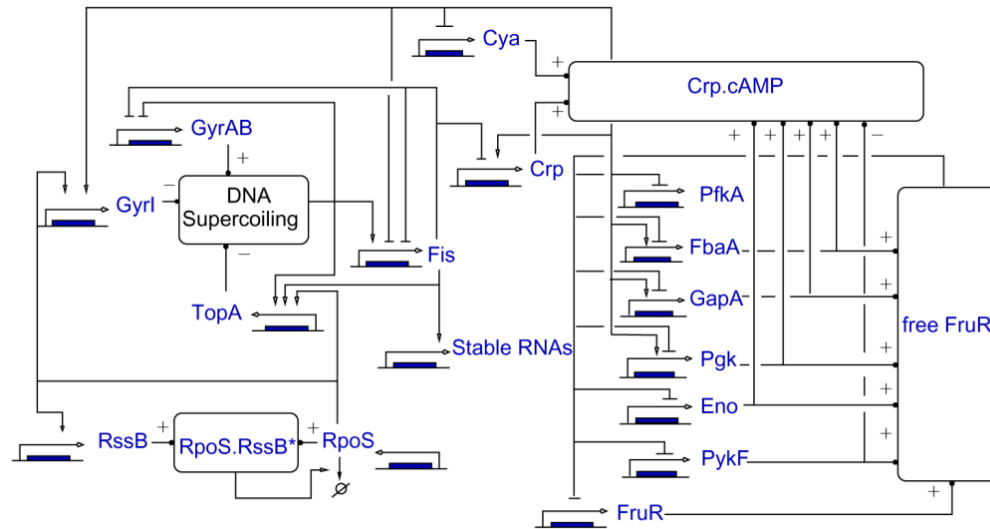
❖ Structure of gene regulatory networks can be obtained by reduction of kinetic model of system of biochemical reactions

Distinct time-scale hierarchies between gene expression and metabolism

Baldazzi *et al.* (2010), *PLoS Comput. Biol.*, 6(6):e1000812



# Structure of gene regulatory networks

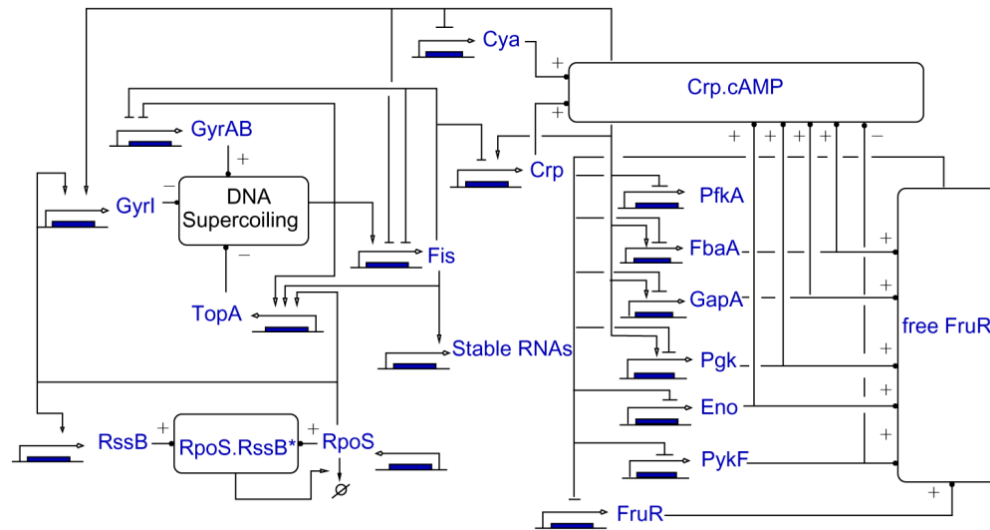


- ❖ Structure of gene regulatory networks can be obtained by reduction of kinetic model of system of biochemical reactions

Distinct time-scale hierarchies between gene expression and metabolism

Baldazzi *et al.* (2010), *PLoS Comput. Biol.*, 6(6):e1000812

# Dynamics of gene regulatory networks



- ❖ **No global view of functioning** of most gene regulatory network available, despite abundant knowledge on network components

Understanding of dynamics requires **mathematical modeling** and **computer analysis and simulation**

# Hierarchy of modeling formalisms

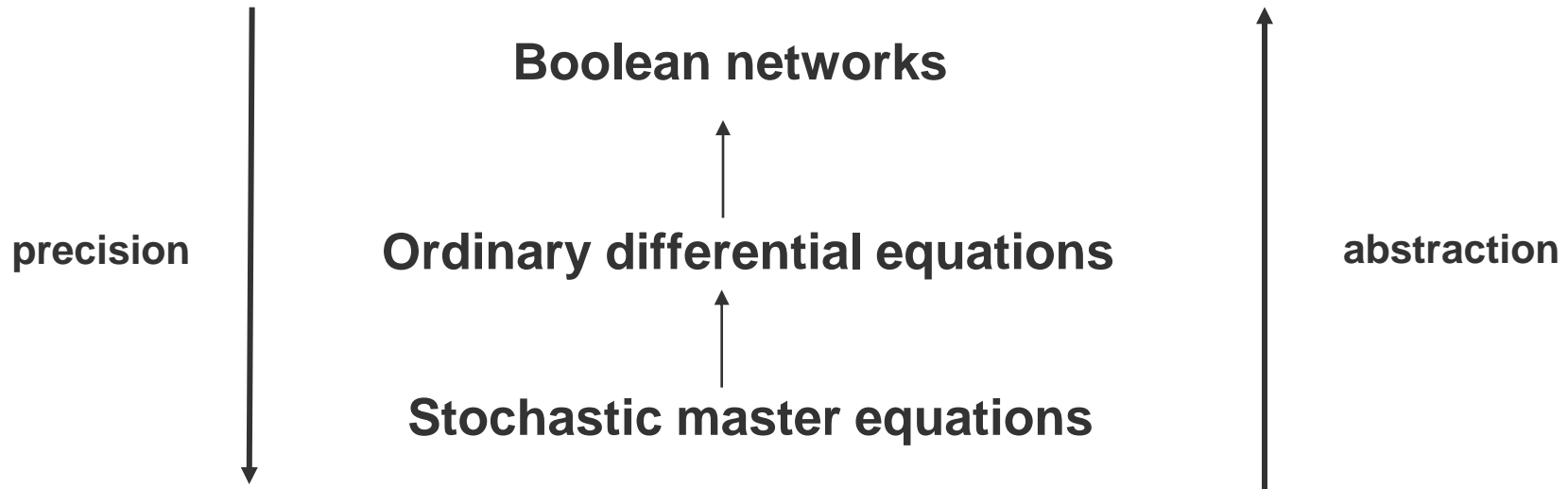
- ❖ Variety of modeling formalisms exist, describing system on different levels of detail

de Jong (2002), *J. Comput. Biol.*, 9(1): 69-105

Hasty *et al.* (2001), *Nat. Rev. Genet.*, 2(4):268-279

Smolen *et al.* (2000), *Bull. Math. Biol.*, 62(2):247-292

Szallasi *et al.* (2006), *System Modeling in Cellular Biology*, MIT Press



# Modeling of genetic regulatory network

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- ❖ Well-established theory for modeling of genetic 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

- ❖ Even in the case of well-studied *E. coli* network!

# Qualitative modeling and simulation

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- ❖ Possible strategies to overcome problems
  - Parameter estimation from experimental data
  - Parameter sensitivity analysis
  - Model simplifications
- ❖ Intuition: essential properties of network dynamics **robust** against reasonable model simplifications
- ❖ **Qualitative** modeling and simulation of large and complex genetic regulatory networks using **simplified** models

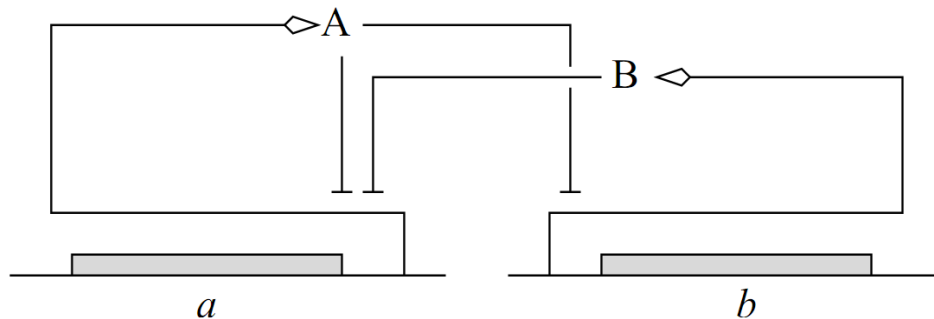
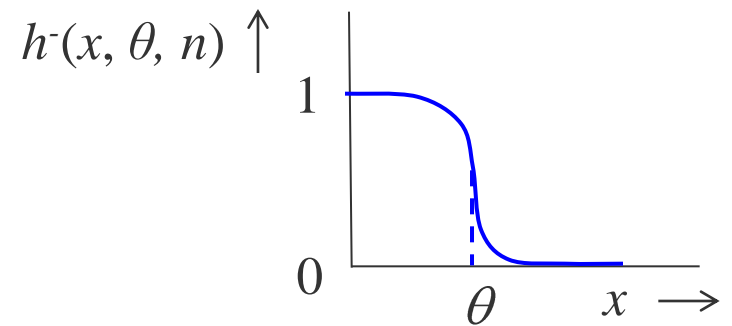
de Jong, Gouzé *et al.* (2004), *Bull. Math. Biol.*, 66(2):301-40
- ❖ Relation with discrete, logical models of gene regulation

Thomas and d'Ari (1990), *Biological Feedback*, CRC Press  
Kauffman (1993), *The Origins of Order*, Oxford University Press

# Ordinary differential equation models

- ❖ Genetic 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  
 $\theta$  : threshold concentration  
 $\kappa, \gamma$  : rate constants  
 $n$  : steepness parameter

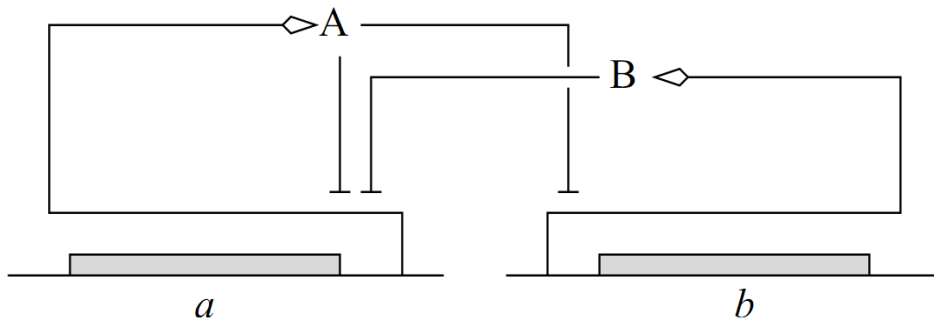
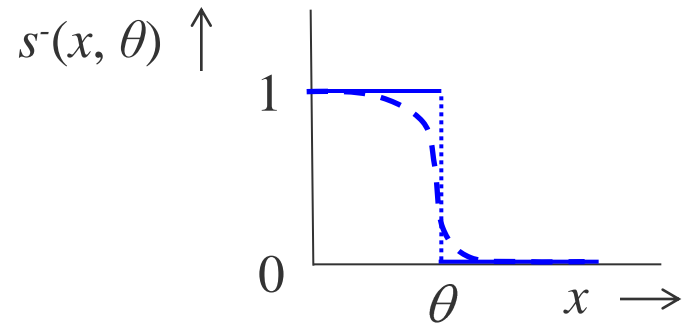
- ❖ Expressions of sigmoid functions account for **combinatorial control** of gene expression (AND, OR, NOR, ...)

# 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  
 $\theta$  : threshold concentration  
 $\kappa, \gamma$  : rate constants

- ❖ **Piecewise-linear (PL) DE models of genetic regulatory networks**

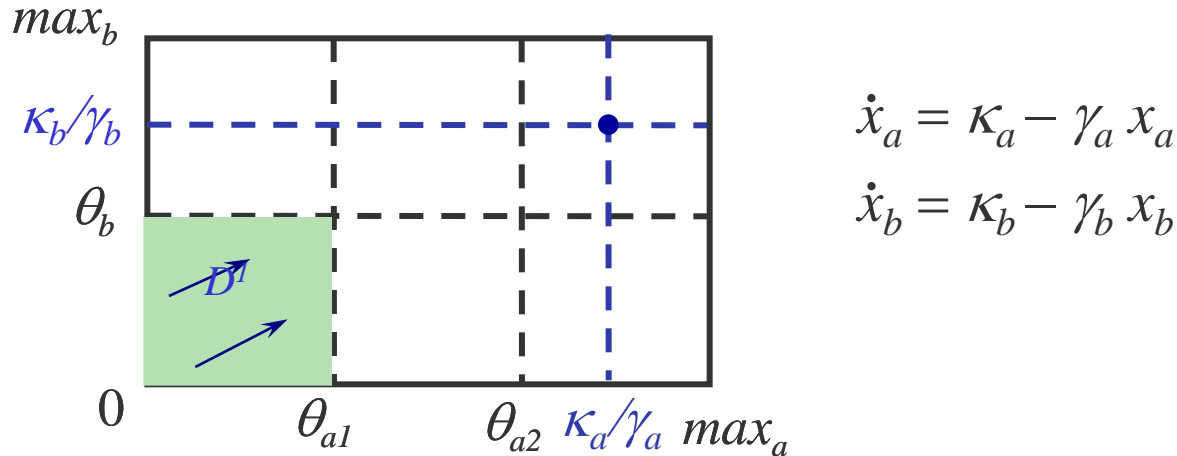
Glass and Kauffman (1973), *J. Theor. Biol.*, 39(1):103-29



# Mathematical analysis of PL models

## ❖ Analysis of local dynamics of PL models

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



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

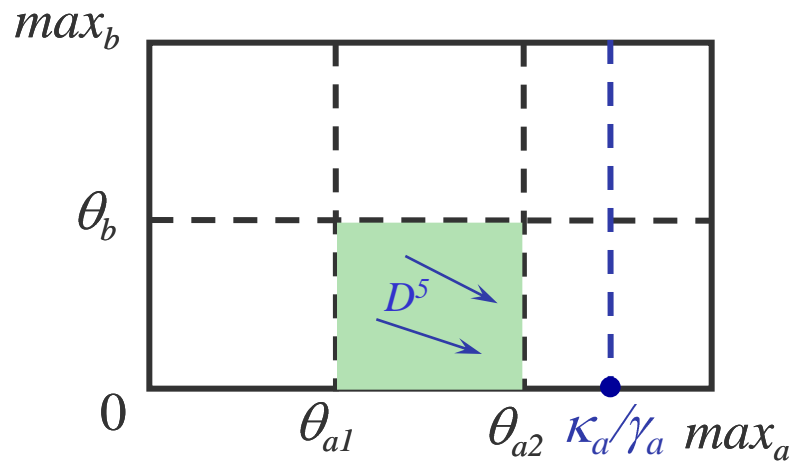
$$\dot{x}_b = \kappa_b s^-(x_a, \theta_{a1}) - \gamma_b x_b$$

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



$$\dot{x}_a = \kappa_a - \gamma_a x_a$$

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

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

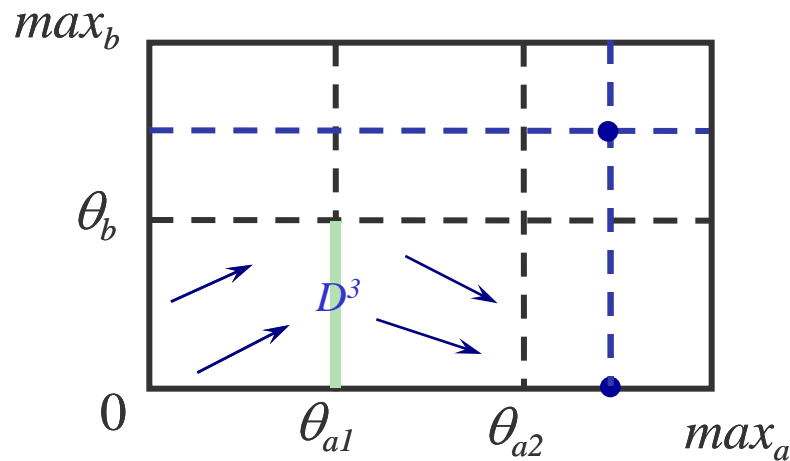
$$\dot{x}_b = \kappa_b s^-(x_a, \theta_{a1}) - \gamma_b x_b$$

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 ...



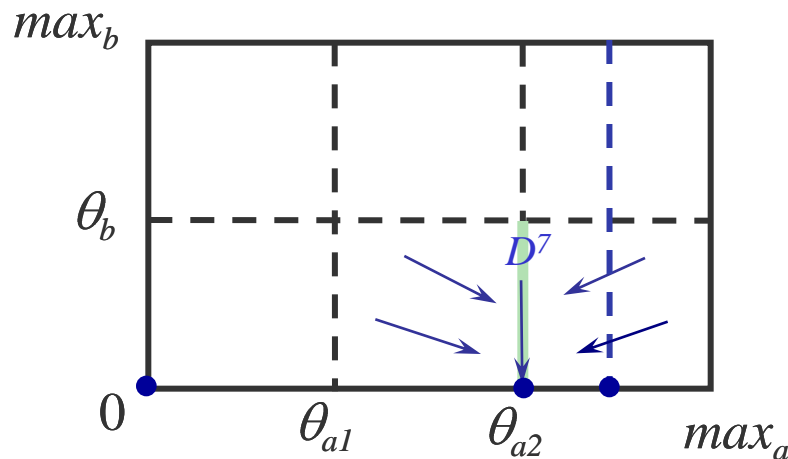
$$\dot{x}_a = \kappa_a s^-(x_a, \theta_{a2}) s^-(x_b, \theta_b) - \gamma_a x_a$$

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

# Mathematical analysis of PL models

## ❖ Analysis of local dynamics of PL models

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



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

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

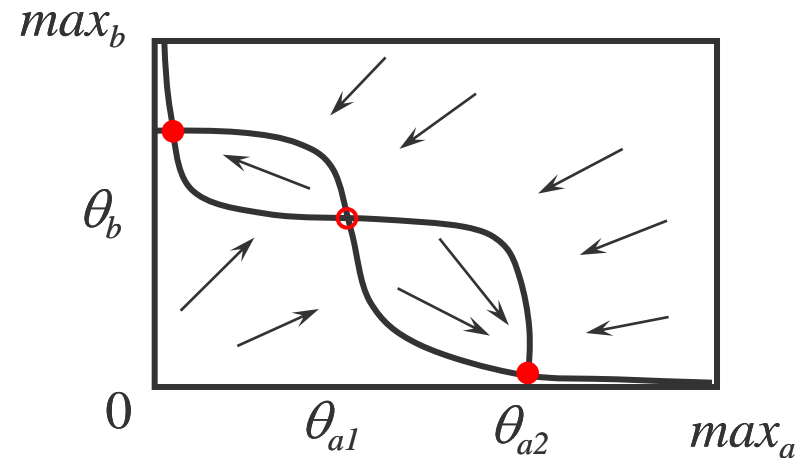
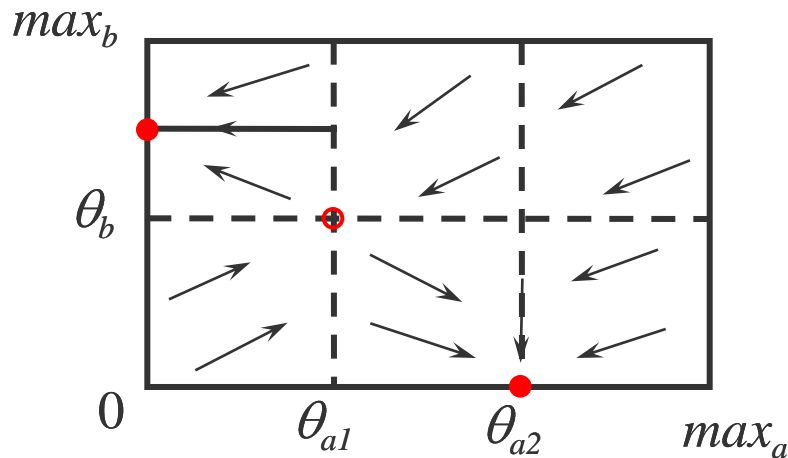
## ❖ Extension of PL differential **equations** to differential **inclusions** using Filippov approach

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

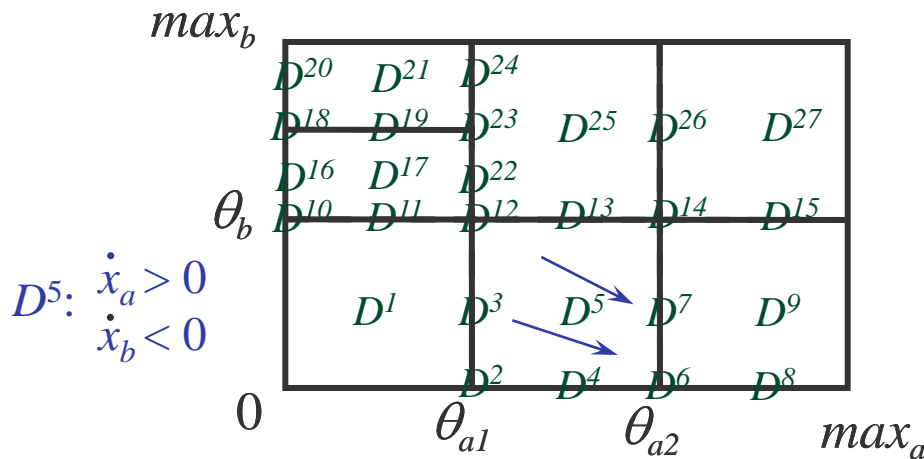
PL approximation preserves bistability of cross-inhibition network



# Qualitative analysis of PL models

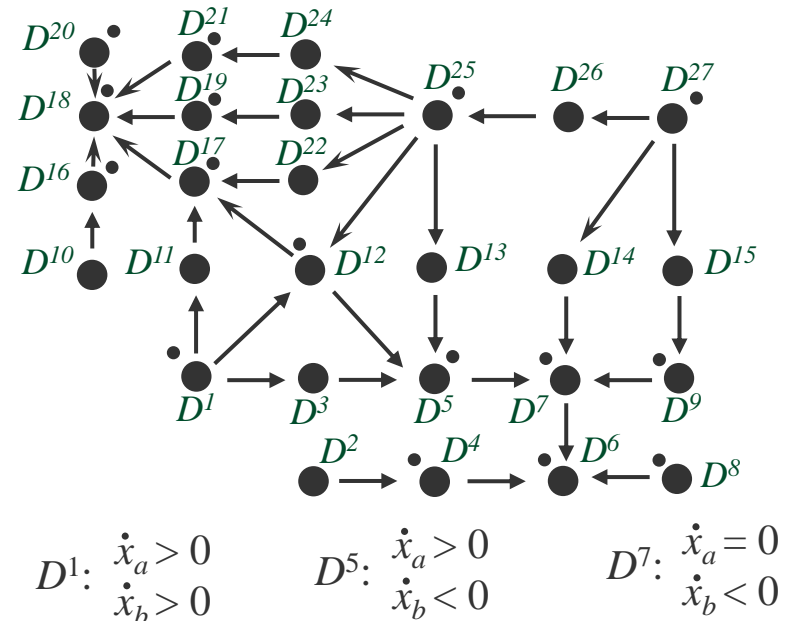
- ❖ State space can be partitioned into regions with **unique** derivative sign pattern
- ❖ **Qualitative abstraction** yields state transition graph that provides discrete picture of continuous dynamics

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



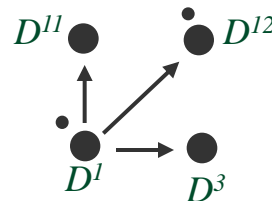
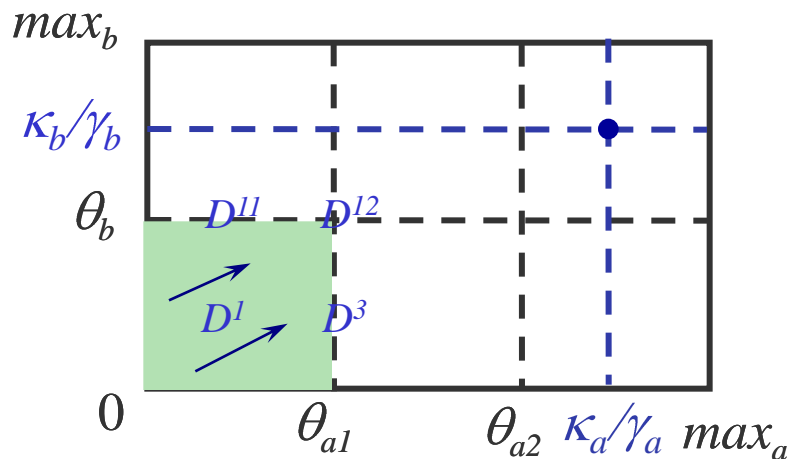
de Jong et al. (2004), *Bull. Math. Biol.*, 66(2):301-40

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



# 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



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

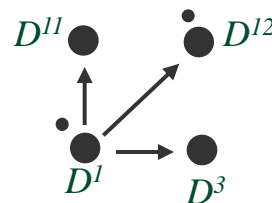
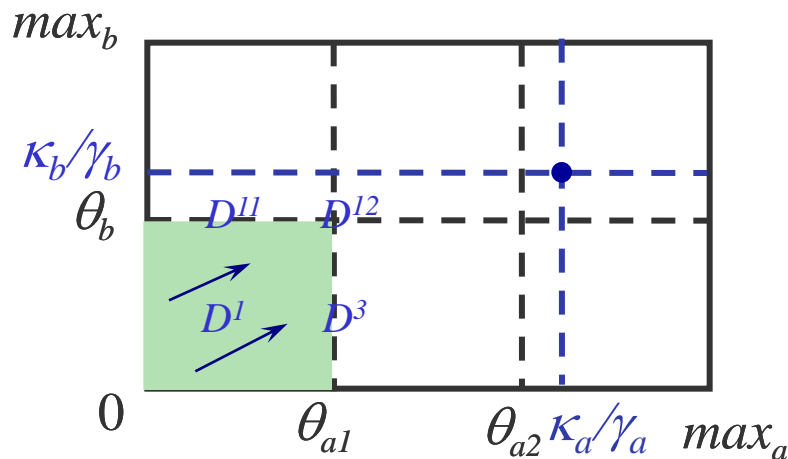
$$0 < \theta_b < \kappa_b/\gamma_b < max_b$$

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



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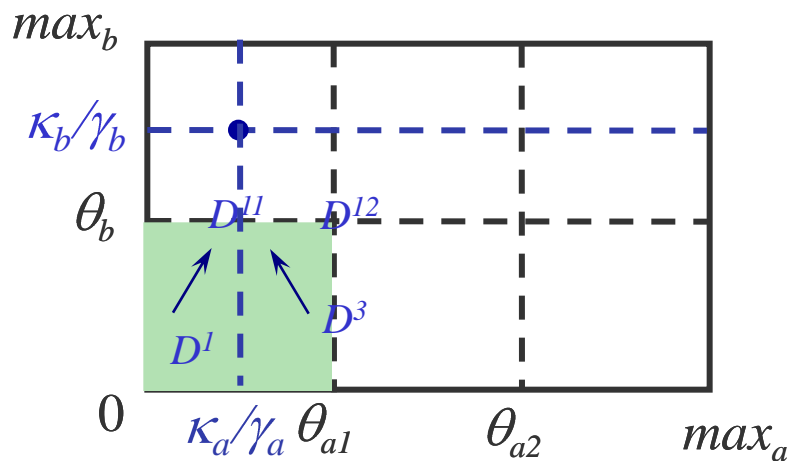
$$0 < \theta_{a1} < \theta_{a2} < \kappa_a/\gamma_a < \max_x$$

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

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

# Qualitative analysis of PL models

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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

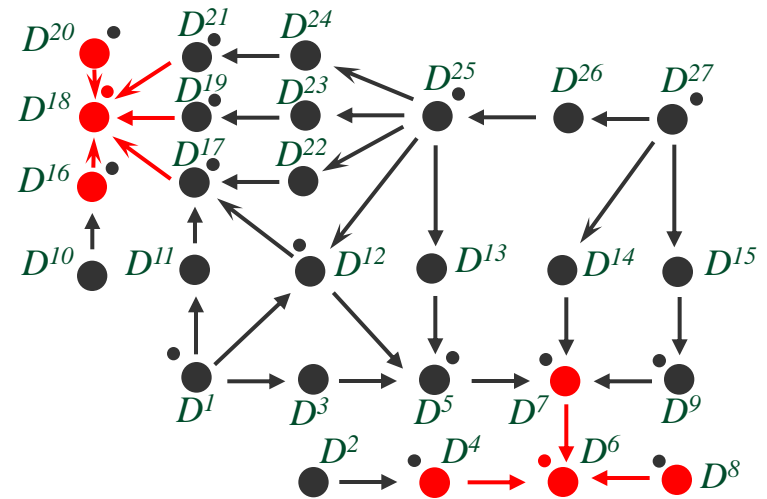
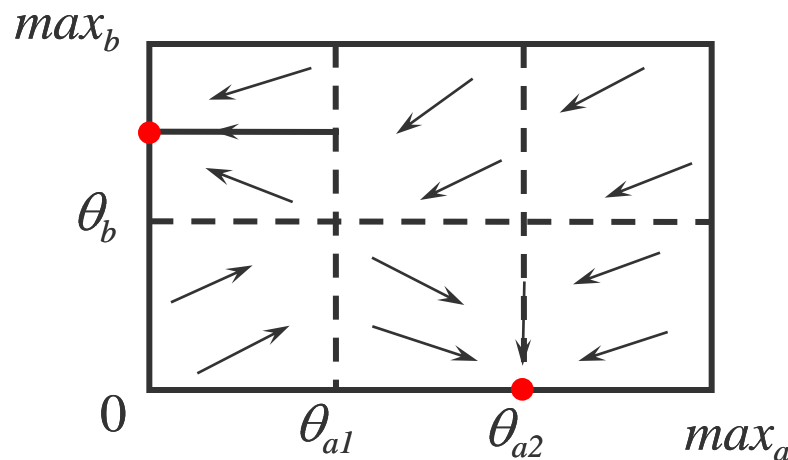
## ❖ Analysis of **steady states** and **limit cycles** of PL models

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

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

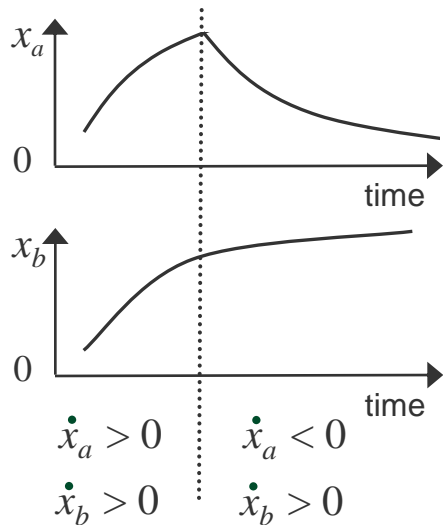
Glass and Pasternack (1978), *J. Math Biol.*, 6(2):207-23

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

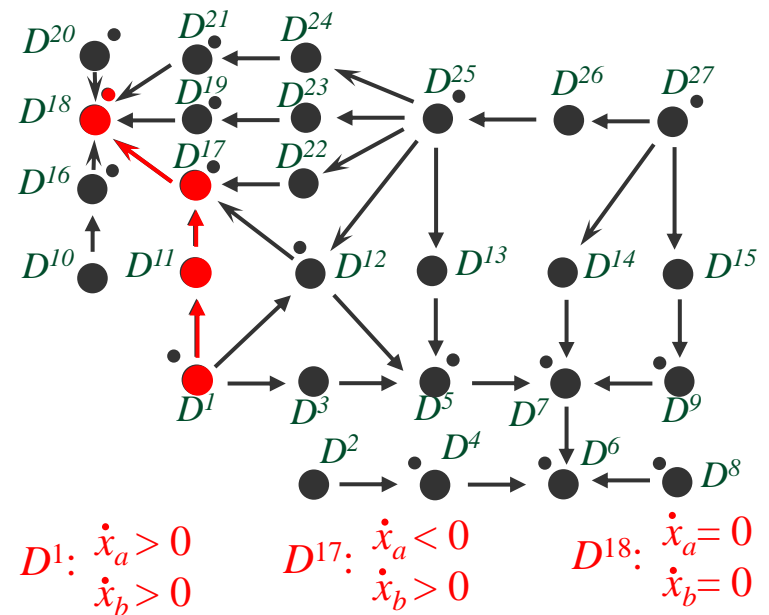


# Use of state transition graph

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



Consistency?  
Yes



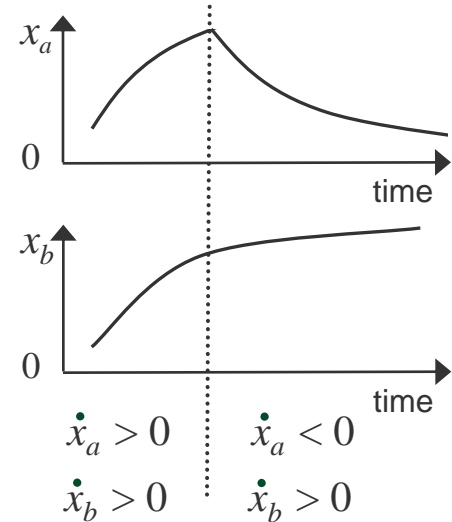
- ❖ Need for automated and efficient tools for model validation

# 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

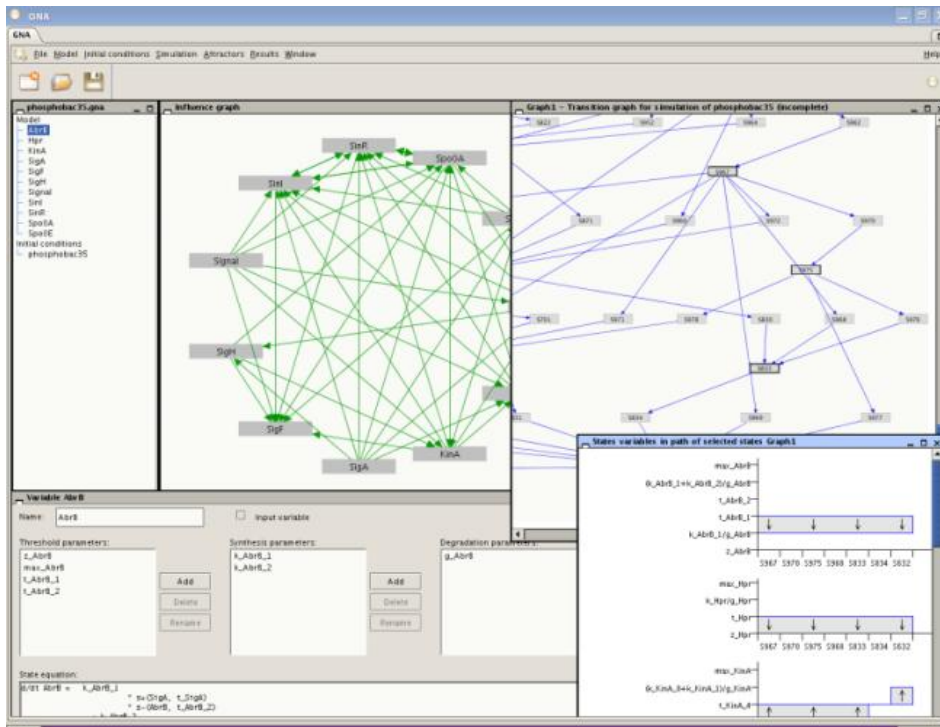
Efficient computer tools available for model checking

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)**

Distribution by  
Genostar SA



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

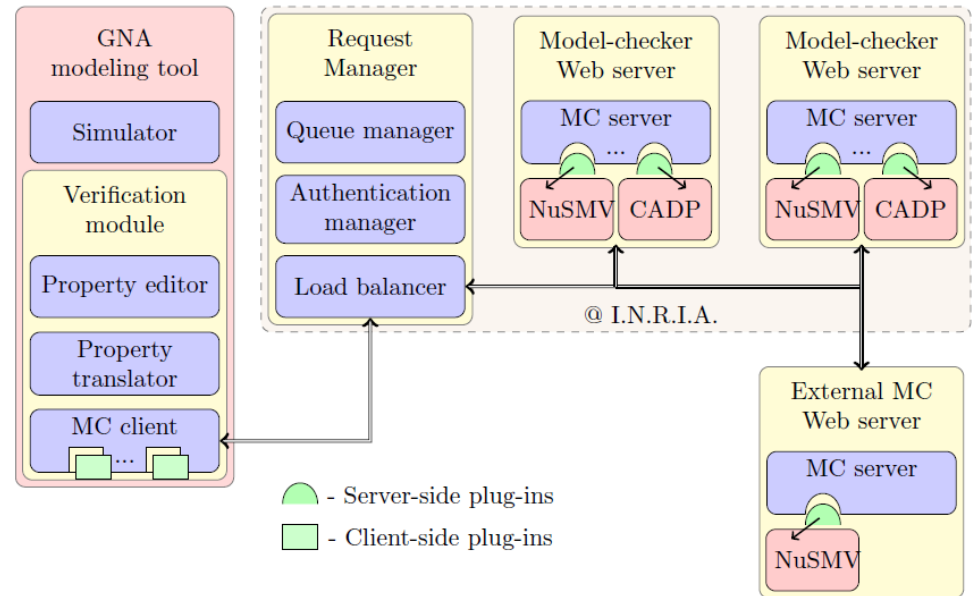
Mateescu *et al.* (2010),  
*Theor. Comput. Sci.*, in press

- Develop temporal-logic patterns 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*

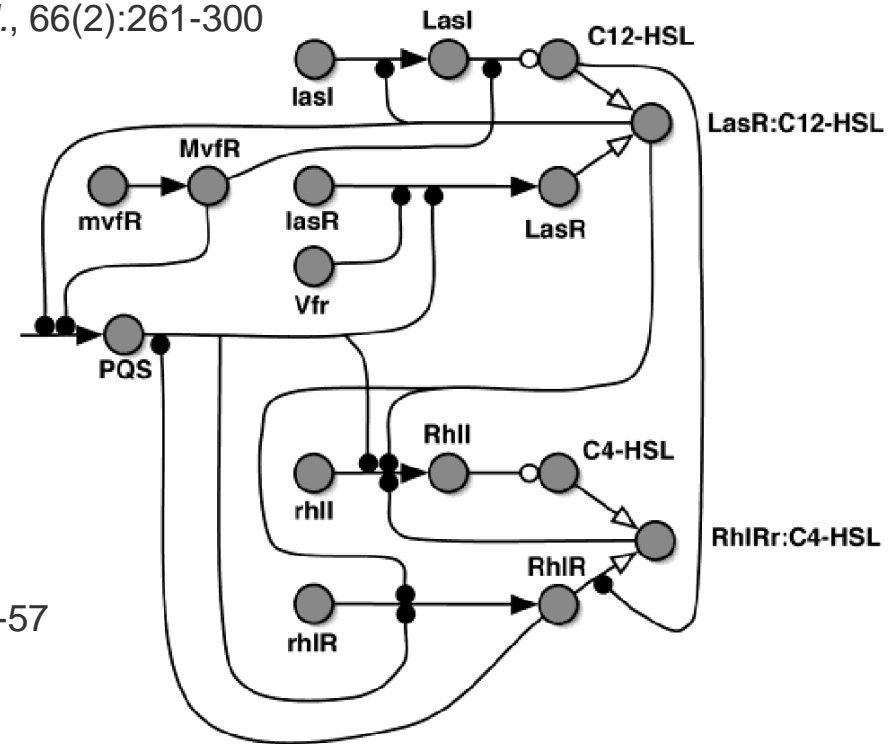
de Jong, Geiselman *et al.* (2004), *Bull. Math. Biol.*, 66(2):261-300

- 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



# Escherichia coli

❖ Enteric bacterium *Escherichia coli* has been most-studied organism in biology

« All cell biologists have two cells of interest: the one they are studying and *Escherichia coli* »

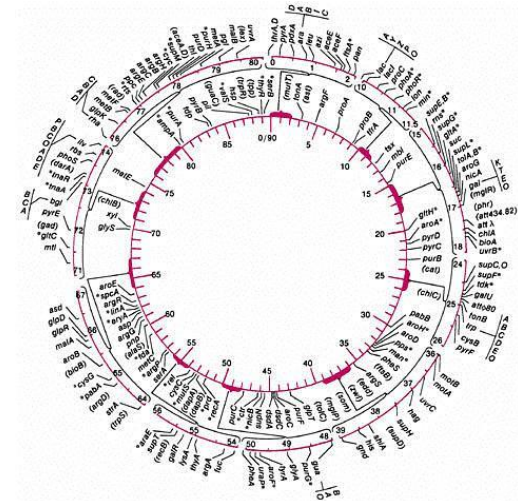
Schaechter and Neidhardt (1996), in: *Escherichia coli and Salmonella*, ASM Press, 4



$10^7$  bacteria



2  $\mu$ m

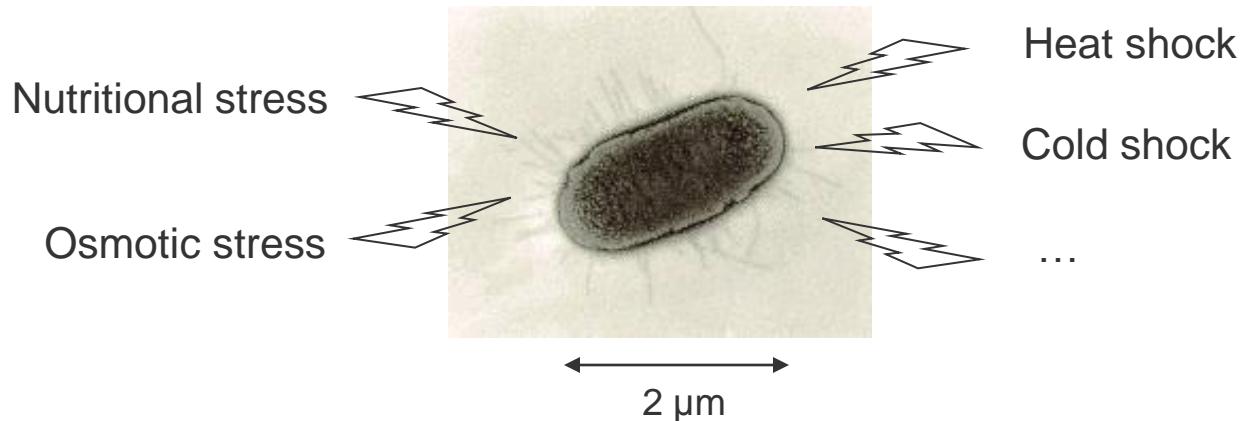


4300 genes

# Stress responses in *Escherichia coli*

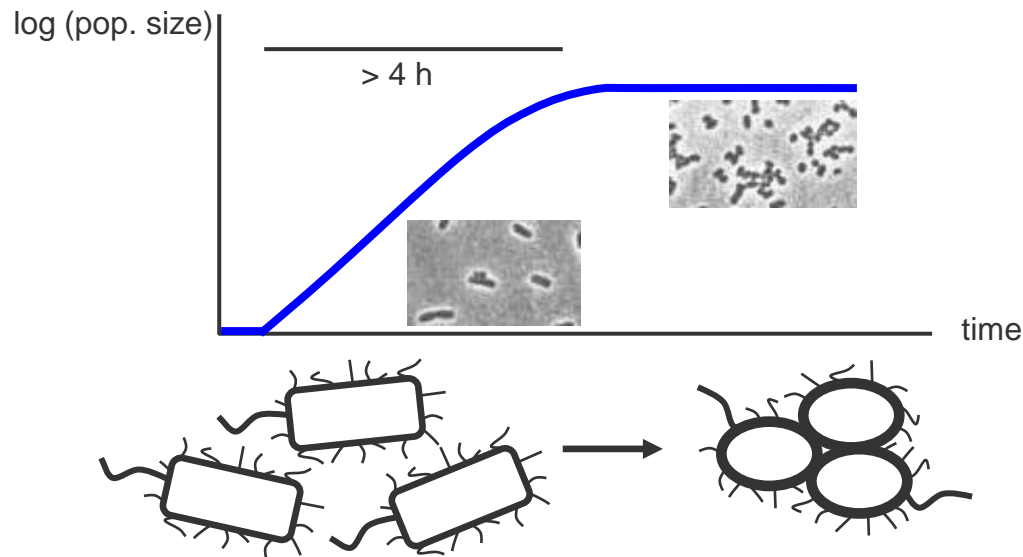
- ❖ Enterobacterium *E. coli* is able to adapt to a variety of stresses in its environment
  - Model organism for understanding of decision-making processes in single-cell organisms
  - Model organism for understanding adaptation of pathogenic bacteria to their host

Storz and Hengge-Aronis (2000), *Bacterial Stress Responses*, ASM Press



# *E. coli* response to carbon starvation

- ❖ Response of *E. coli* to carbon starvation conditions: transition from **exponential phase** to **stationary phase**



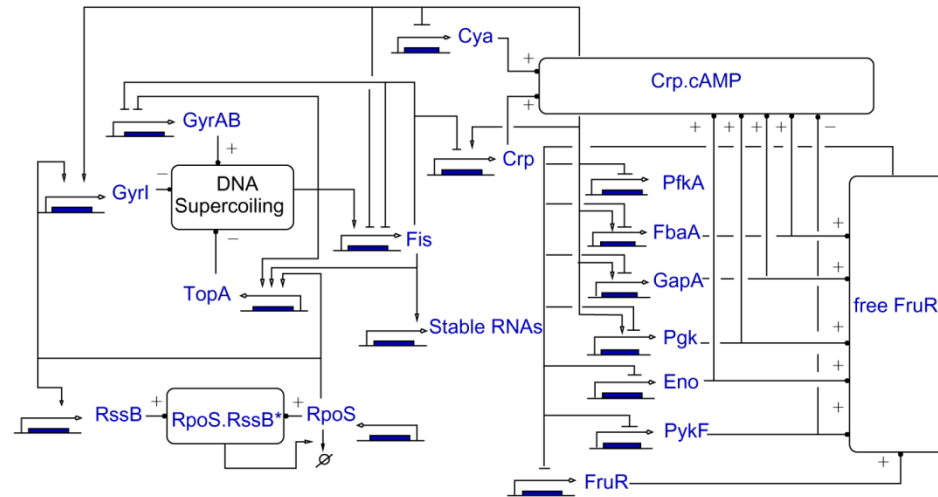
- ❖ Growth transition is accompanied by profound changes in gene expression, allowing cell to adjust its functioning to stress conditions

Storz and Hengge-Aronis (2000), *Bacterial Stress Responses*, ASM Press

# Modeling of carbon starvation network

- ❖ Can we understand how gene regulatory network controls adaptation in response to carbon starvation?

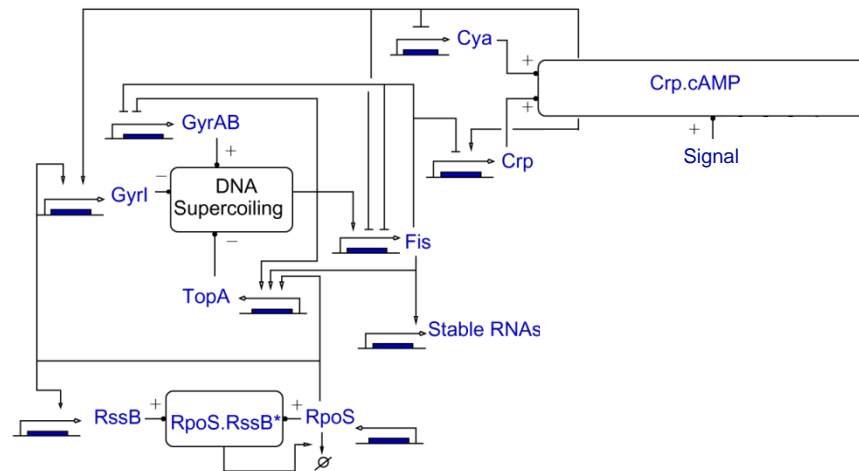
Network senses carbon source availability and **global regulators** coordinate adaptive response of bacteria



# Modeling of carbon starvation network

- ❖ Can we understand how gene regulatory network controls adaptation in response to carbon starvation?

Network senses carbon source availability and **global regulators** coordinate adaptive response of bacteria



- ❖ Development of qualitative model of network

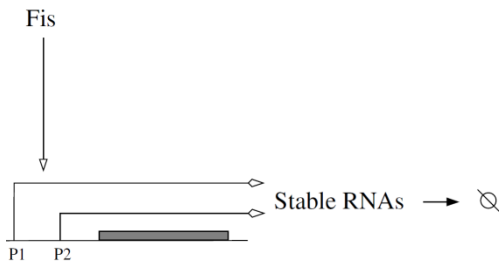
Translation of network diagram into PL formalism (regulatory logic)

Ropers *et al.* (2006), *Biosystems*, 84(2):124-152; Ropers *et al.* (2010), in press

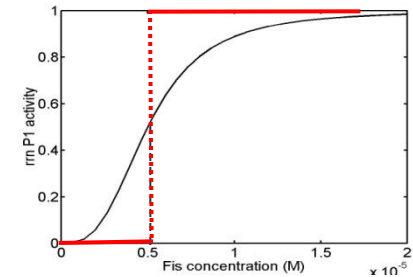
# Development of PL model

## ❖ Translation of network diagrams into PL models

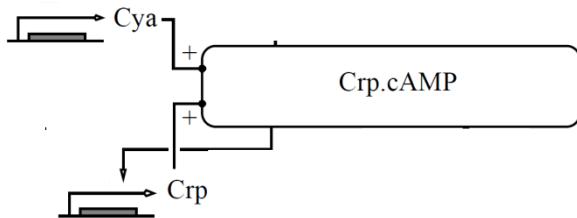
- Straightforward for direct interactions...



$$\dot{x}_n = \kappa_n^2 + \kappa_n^1 s^+(x_f, \theta_f) - \gamma_n x_n$$

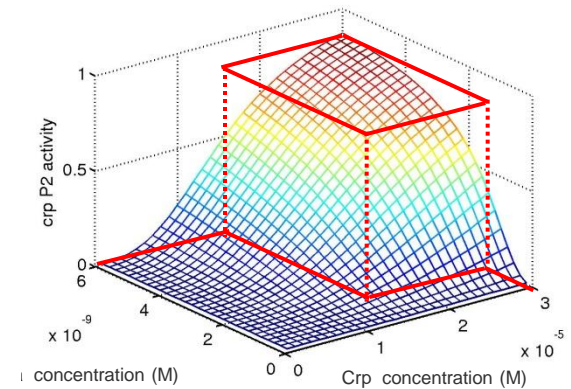


- ... but also possible for indirect interactions



$$\dot{x}_y = \kappa_y^1 + \kappa_y^2 - \gamma_y x_y$$

$$\dot{x}_c = \kappa_c^1 + \kappa_c^2 s^+(x_c, \theta_c^1) s^+(x_y, \theta_y^1) - \gamma_c x_c$$





# PL model of carbon starvation network

$$\begin{aligned}
 \dot{u}_s &= 0 \\
 \dot{x}_y &= \kappa_y^1 + \kappa_y^2 (1 - s^+(x_c, \theta_c^2) s^+(x_y, \theta_y^2) s^+(u_s, \theta_s)) - \gamma_y x_y \\
 \dot{x}_c &= \kappa_c^1 + \kappa_c^2 s^-(x_f, \theta_f^2) s^+(x_c, \theta_c^1) s^+(x_y, \theta_y^1) s^+(u_s, \theta_s) + \kappa_c^3 s^-(x_f, \theta_f^1) - \gamma_c x_c \\
 \dot{x}_f &= \kappa_f^1 (1 - s^+(x_c, \theta_c^1) s^+(x_y, \theta_y^1) s^+(u_s, \theta_s)) s^-(x_f, \theta_f^6) \\
 &\quad + \kappa_f^2 s^+(x_a, \theta_a^1) s^-(x_i, \theta_i^1) s^-(x_t, \theta_t^1) s^-(x_f, \theta_f^6) \\
 &\quad \times (1 - s^+(x_c, \theta_c^1) s^+(x_y, \theta_y^1) s^+(u_s, \theta_s)) - \gamma_f x_f \\
 \dot{x}_a &= \kappa_a (1 - s^+(x_a, \theta_a^2) s^-(x_i, \theta_i^2) s^-(x_t, \theta_t^2)) s^-(x_f, \theta_f^4) - \gamma_a x_a \\
 \dot{x}_i &= \kappa_i s^+(x_c, \theta_c^1) s^+(x_y, \theta_y^1) s^+(u_s, \theta_s) s^+(x_o, \theta_o) - \gamma_i x_i \\
 \dot{x}_o &= \kappa_o - (\gamma_o + k_7 s^+(x_b, \theta_b) s^-(u_s, \theta_s)) x_o \\
 \dot{x}_b &= \kappa_b^1 + \kappa_b^2 s^+(x_o, \theta_o) - \gamma_b x_b \\
 \dot{x}_t &= \kappa_t^1 s^+(x_a, \theta_a^3) s^-(x_i, \theta_i^3) s^-(x_t, \theta_t^3) s^+(x_f, \theta_f^5) + \kappa_t^2 s^+(x_o, \theta_o) - \gamma_t x_t \\
 \dot{x}_n &= \kappa_n^1 s^+(x_f, \theta_f^3) + \kappa_n^2 - \gamma_n x_n
 \end{aligned}$$

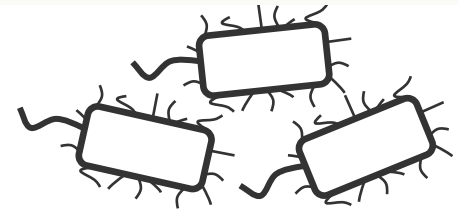
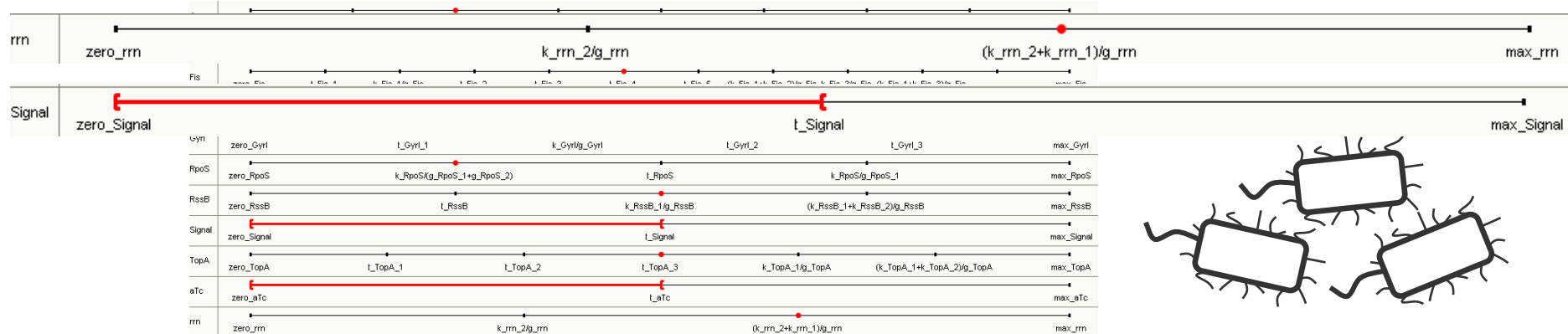
- ❖ PL models supplemented with inequality constraints on parameter values

Inequality constraints inferred from experimental literature

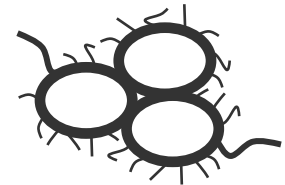
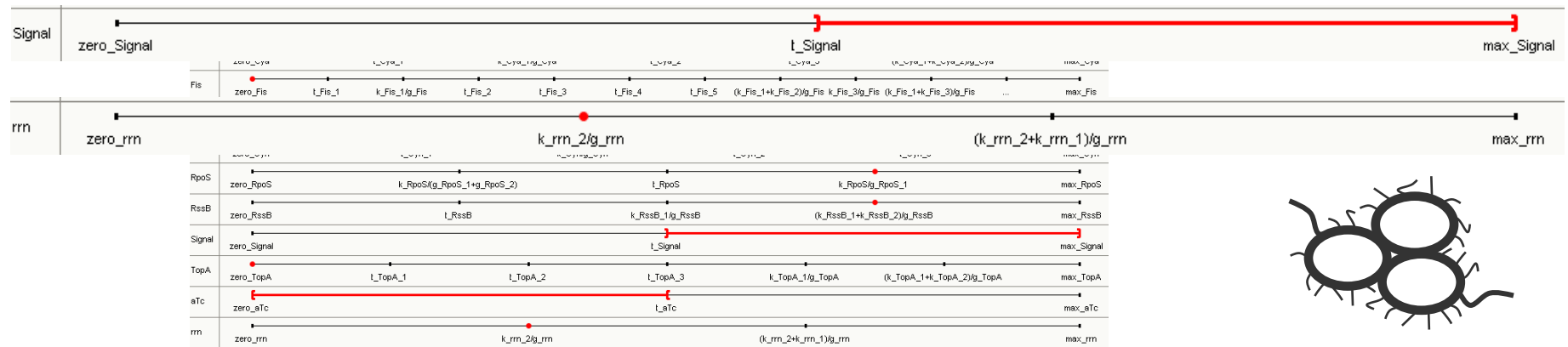
# Attractors of stress response network

## ❖ Analysis of attractors of PA model: two **steady states**

- **Stable** steady state, corresponding to exponential-phase conditions

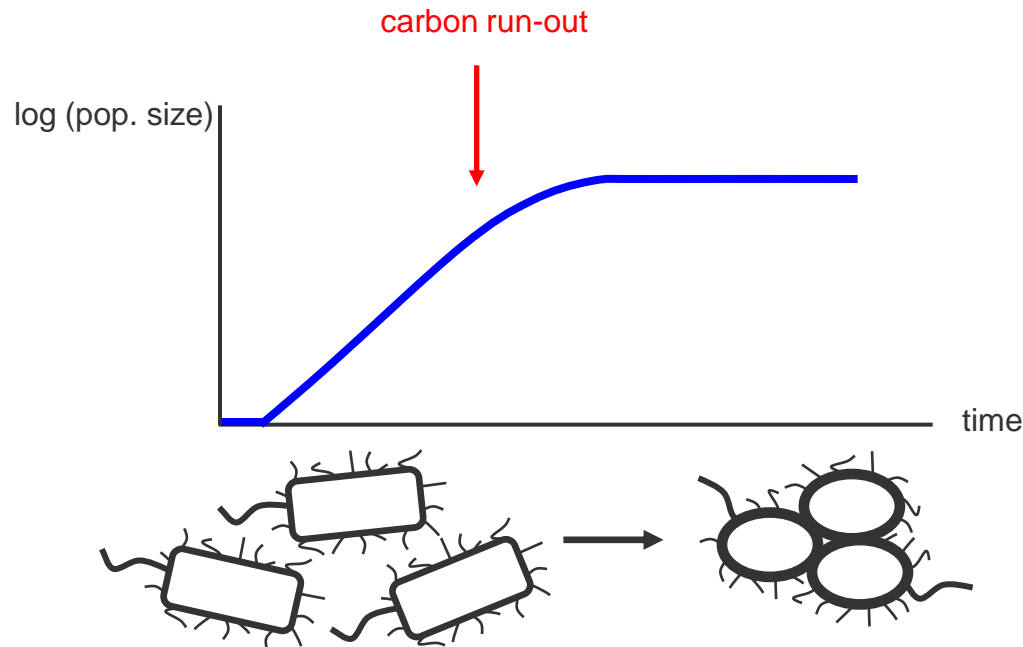


- **Stable** steady state, corresponding to stationary-phase conditions



# Transition to stationary phase

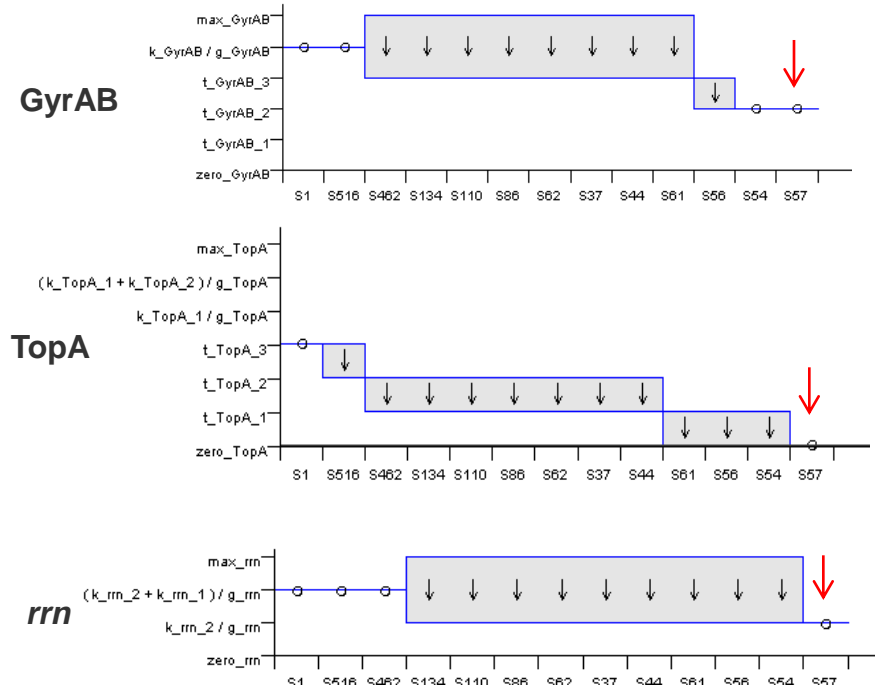
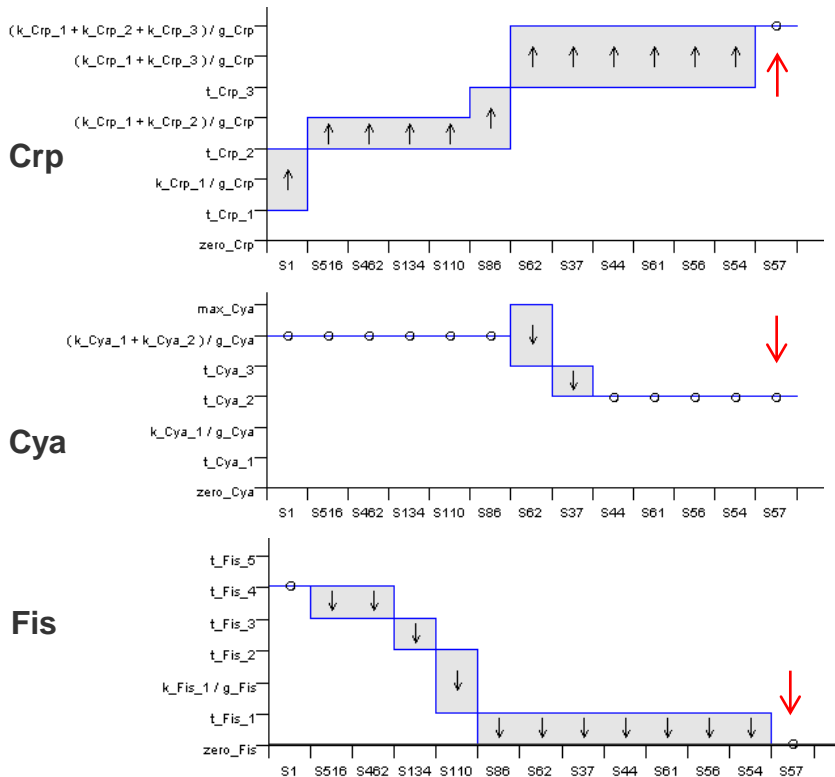
- ❖ Does model reproduce transition from exponential phase to stationary phase upon carbon starvation?



# Qualitative simulation of network

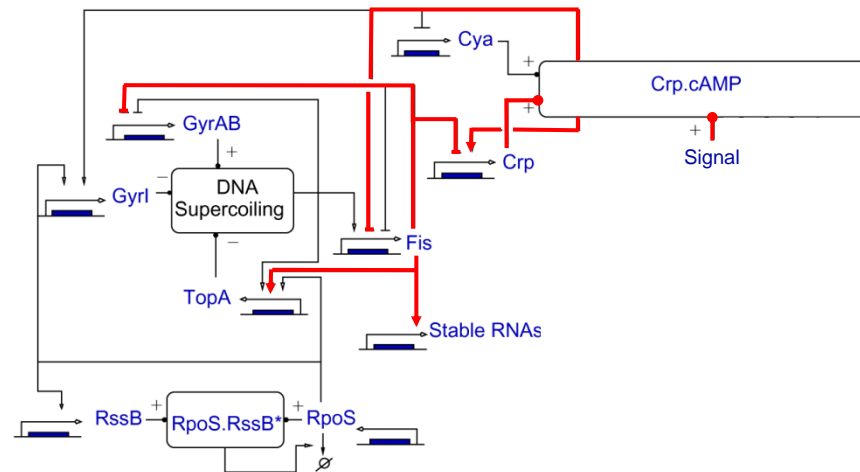
## Simulation of transition from exponential to stationary phase

State transition graph with 851 states starting from exponential phase, all paths converge to **stationary-phase steady state** upon stress signal



# Insight into carbon starvation response

- ❖ Sequence of **qualitative events** leading to adjustment of growth of cell after carbon starvation signal

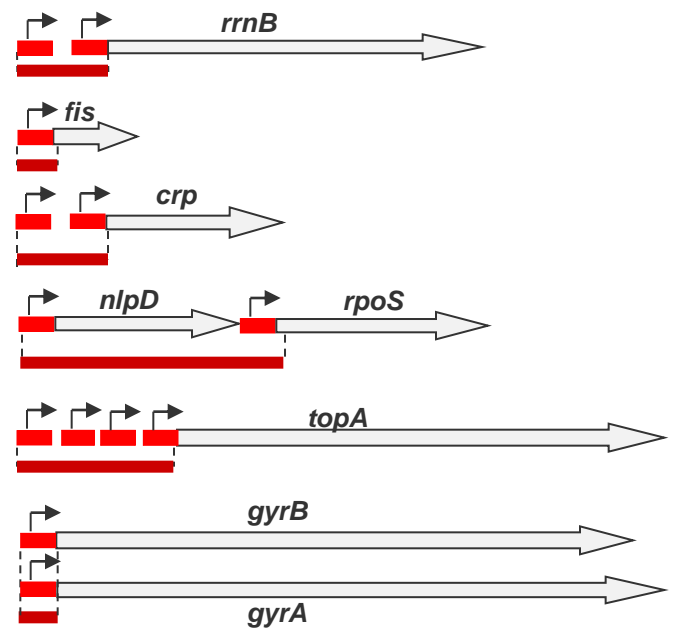


- ❖ Central role for **mutual inhibition** of Fis and Crp, the two major regulators of the cell

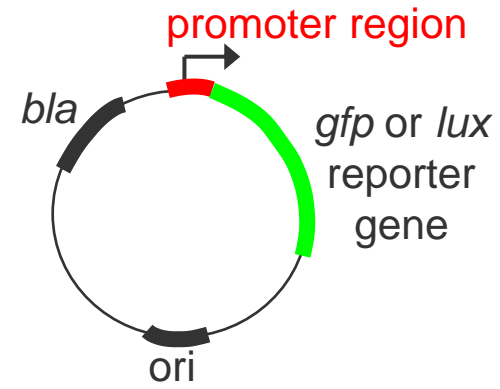
Cross inhibition functions as toggle switch for adjusting expression level of genes controlled by Fis and Crp, switch pulled by stress signal

# Reporter gene systems

- ❖ Simulations yield predictions that cannot be verified with currently available experimental data
- ❖ Use of **reporter gene systems** to monitor gene expression

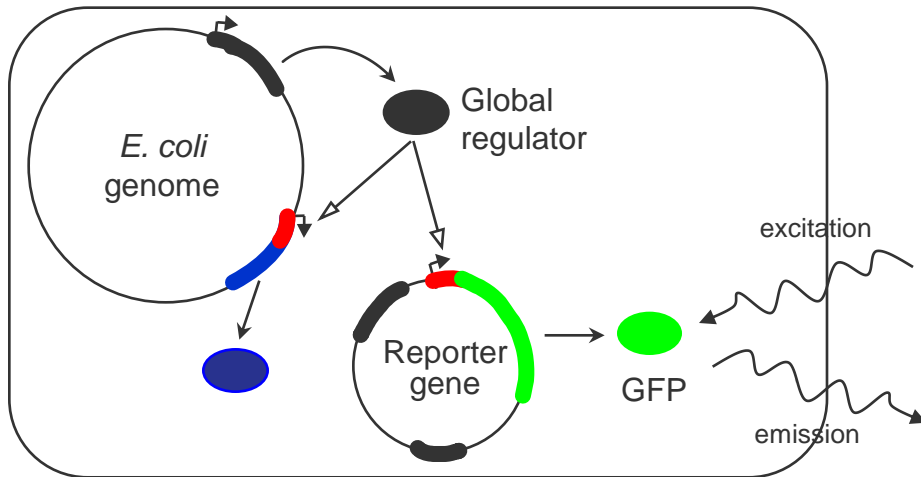


cloning promoter regions on plasmid



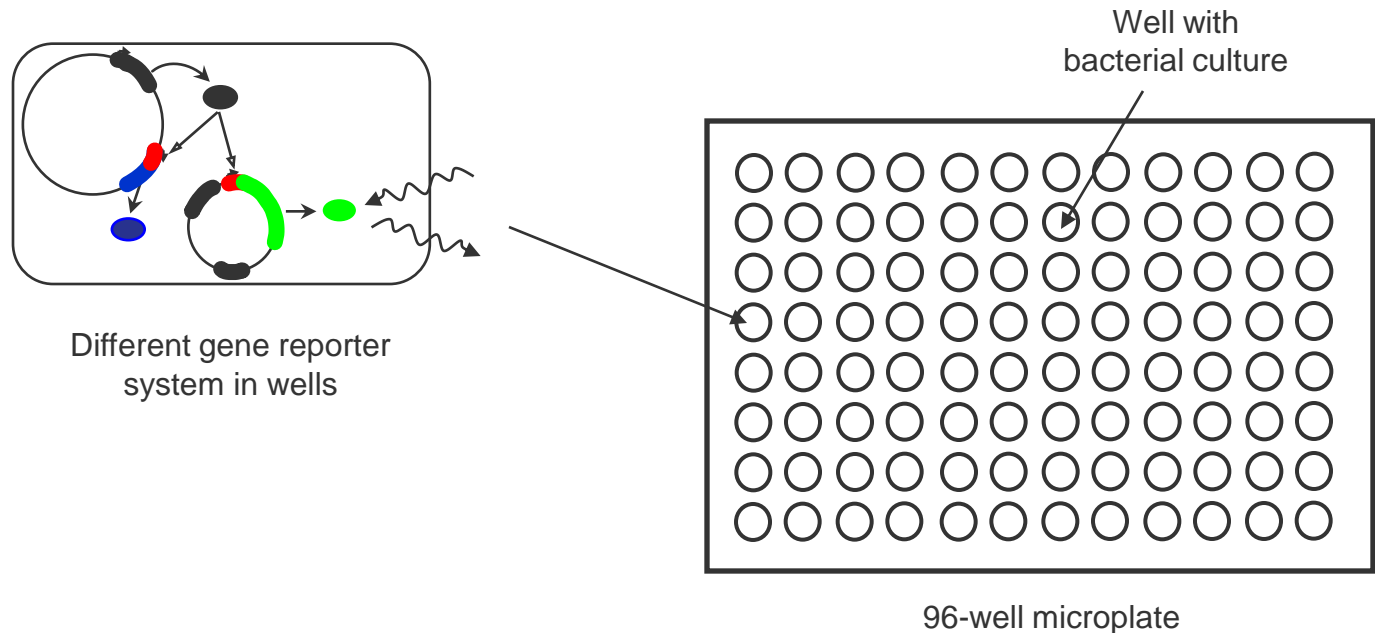
# Real-time monitoring of gene expression

- ❖ Integration of reporter gene systems into bacterial cell



# Real-time monitoring of gene expression

- ❖ Integration of reporter gene systems into bacterial cell



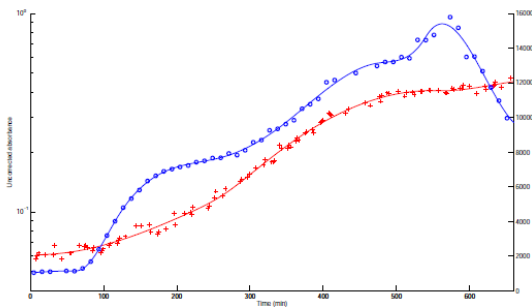
- ❖ Use of automated microplate reader to monitor in parallel in single experiment expression of different reporter genes



# Reporter gene measurements

- ❖ High-precision measurements of changes in gene expression on population level in response to environmental perturbations
  - Measurement of absorbance, fluorescence, luminescence
  - About 100 data points over an interval of 10 hours
- ❖ Treatment of raw data
  - Outlier detection, regression spline fitting with GCV, background subtraction, confidence intervals via bootstrap, ...

Fluorescence and absorbance data

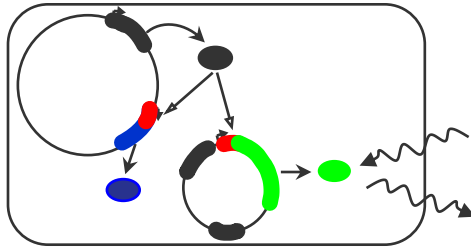


de Jong *et al.* (2010), *BMC Syst. Biol.*, 4:55

# Reporter gene measurements

## ❖ Computation of biological quantities using kinetic models

Reporter protein concentrations and reporter synthesis rates  
(proportional to mRNA concentrations)

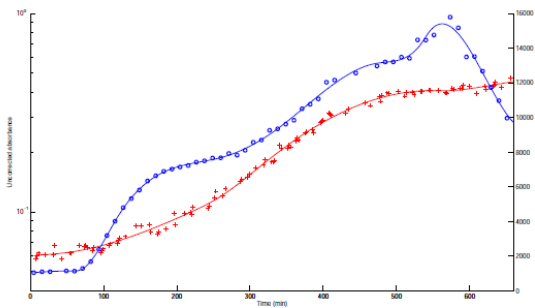


$$\frac{dn(t)}{dt} = \kappa_m f(t) - (\mu(t) + \gamma_n) n(t)$$

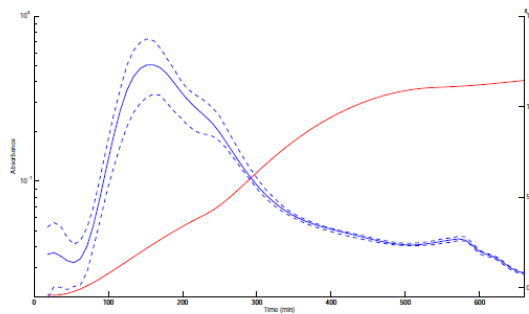
$$\frac{dq(t)}{dt} = \kappa_p n(t) - (\mu(t) + \gamma_q) q(t)$$

$$\frac{dr(t)}{dt} = \kappa_r (q(t) - r(t)) - (\mu(t) + \gamma_r) r(t)$$

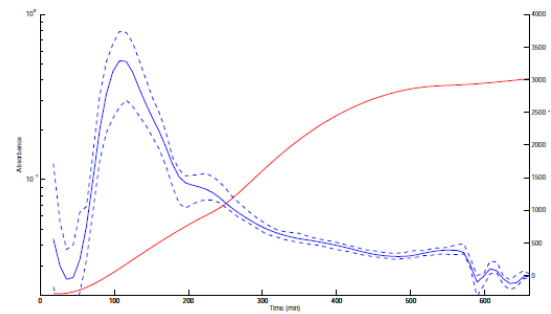
Fluorescence and absorbance data



Fis reporter concentration



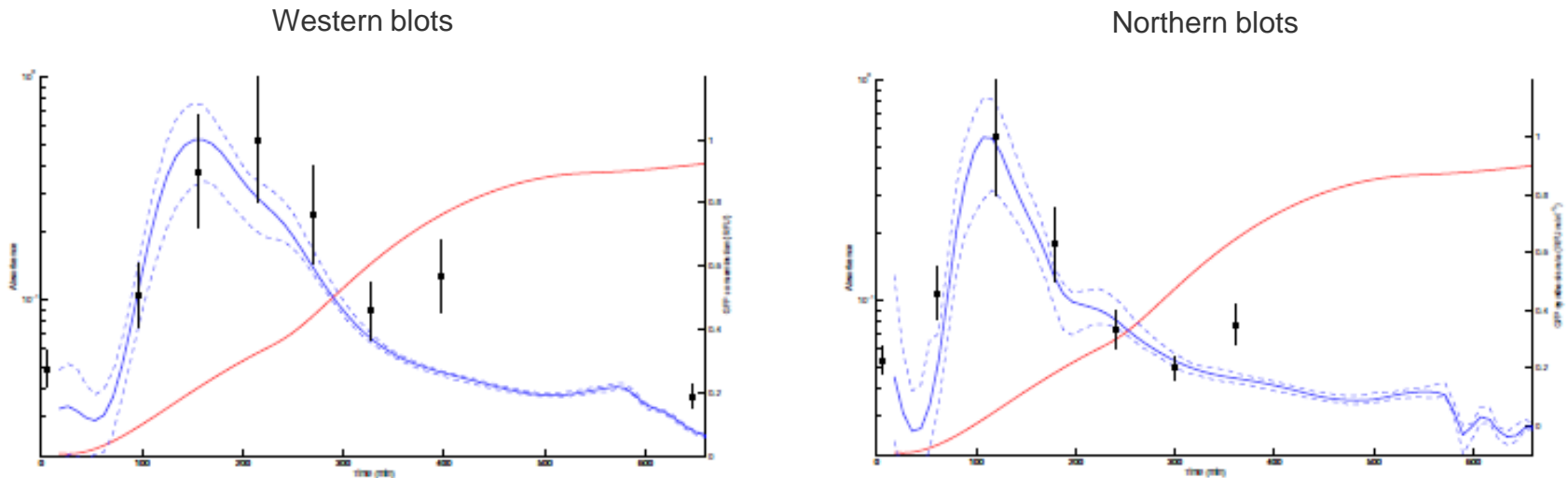
fis reporter mRNA concentration



de Jong *et al.* (2010), *BMC Syst. Biol.*, 4:55

# Validation of reporter gene measurements

- ❖ Good correspondence between (relative) protein concentrations and protein synthesis rates (mRNA concentrations) and direct measurements

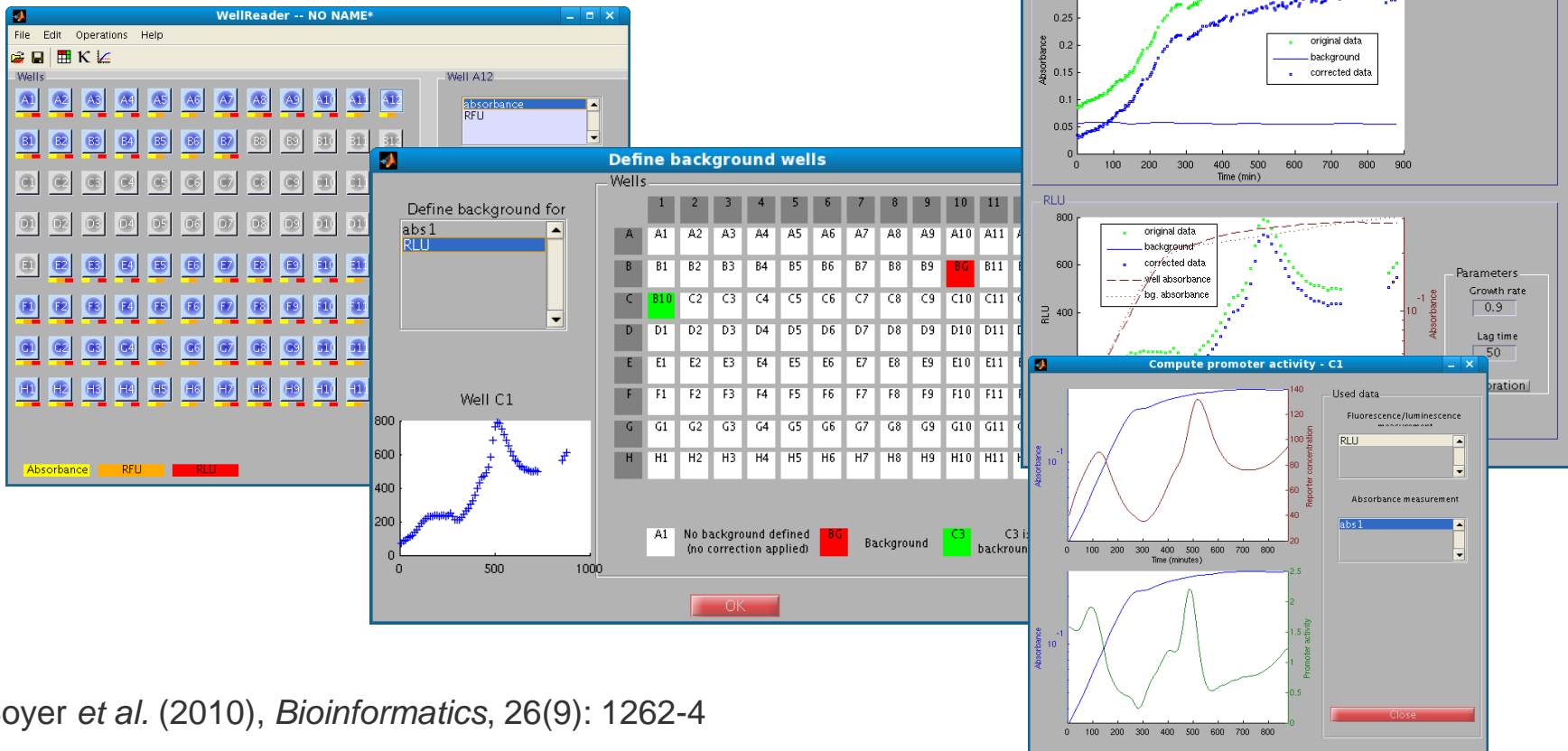


de Jong *et al.* (2010), *BMC Syst. Biol.*, 4:55

- ❖ Corrections for differences in degradation constants slightly improves correspondence

# Analysis of reporter gene expression data

## Wellreader: Matlab program for analysis of reporter gene expression data



Boyer et al. (2010), *Bioinformatics*, 26(9): 1262-4

# Perspectives: towards quantitative models

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- ❖ Qualitative models can help **understand basic principles underlying dynamics** of complex gene regulatory networks

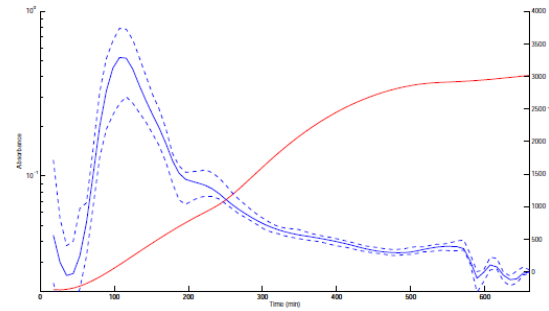
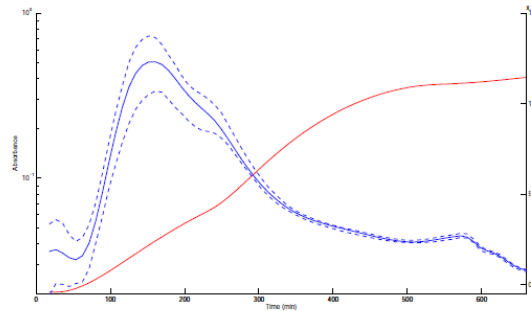
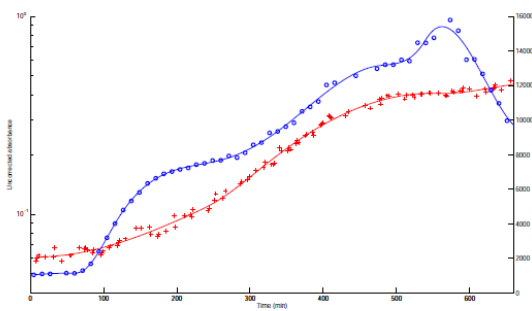
Models provide a coarse-grained picture of the dynamics, but capture the regulatory logic of the network of interactions

- ❖ Biological validation of qualitative models has a long history, and **experimental validation** of specific predictions is increasingly becoming possible

- New **measurement techniques**: fluorescent reporter genes, plate readers (cell populations) and microscopes (individual cells), quantitative proteomics and metabolomics, ...
- New ways to **control biological systems**: overexpression plasmids, microfluidics, synthetic biology, ...

# Perspectives: towards quantitative models

- ❖ Quality of data produced by new experimental techniques makes it increasingly realistic to work with fully quantitative ODE models
  - More accurate representation of biochemical mechanisms
  - More precise predictions
- ❖ Perspective raises new methodological challenges: parameter estimation in large nonlinear ODE models





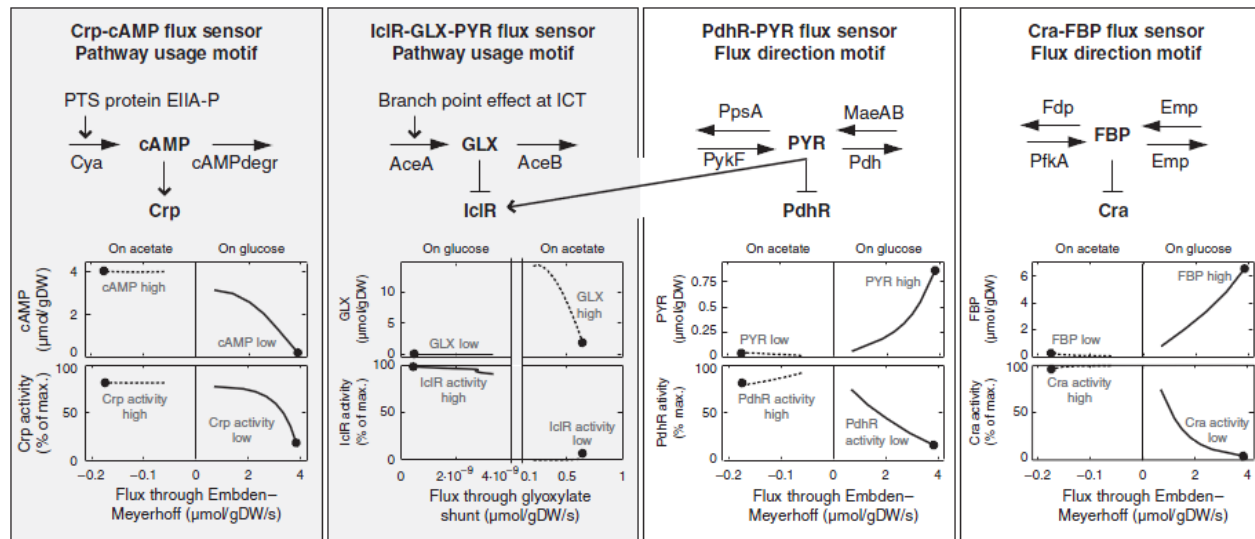


# Perspectives: towards quantitative models

## ❖ Kinetic model with 47 variables and 193 parameters

Parameters estimated from published experimental steady-state data sets for balanced growth on either glucose or acetate

## ❖ Analysis of model shows that adaptation to change in carbon source is achieved by distributed sensing of intracellular fluxes



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



# Perspectives: towards quantitative models

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- ❖ No algorithms that guarantee globally optimal solution for parameter estimation in nonlinear models

Evolutionary algorithms, simulated annealing, genetic algorithms, ...

- ❖ Parameter estimation demands experimental data of sufficient quantity and quality

Common problems: noise, sampling density, unobserved variables, ...

Ashyraliyev et al. (2009), *FEBS J.*, 276:886-902

van Riel (2006), *Brief. Bioinform.*, 7(4):364–74

- ❖ Moreover, models of regulatory networks may be non-identifiable by principle, but ...

... even partially identifiable models may yield interesting results!

# Conclusions

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- ❖ Modeling of genetic regulatory networks in bacteria often hampered by lack of information on parameter values
- ❖ Use of coarse-grained PL models that provide reasonable approximation of dynamics
- ❖ Mathematical methods and computer tools for analysis of qualitative dynamics of PL models
  - Weak information on parameter values (inequality constraints)
- ❖ Use of PL models may gain insight into functioning of large and complex networks
- ❖ PL models provide first idea of qualitative dynamics that may guide modeling by means of quantitative models

# Contributors and sponsors

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Courtesy Guillaume Baptist (2008)

