Qualitative Analysis of Genetic Regulatory Networks: A Model-Checking Approach

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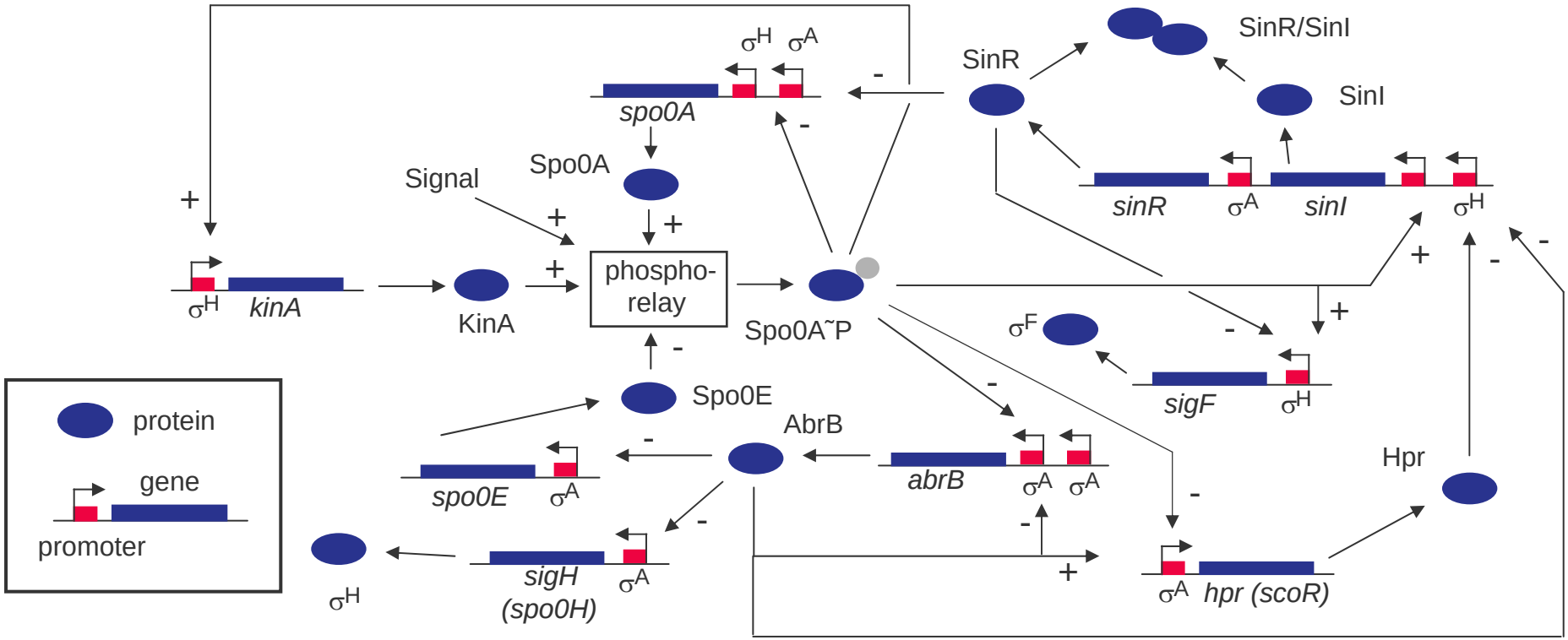
Overview

1. Introduction
2. Qualitative modeling and simulation of genetic regulatory networks
3. Analysis of genetic regulatory networks using a model-checking approach
4. Discussion and conclusions

Genetic regulatory networks

- **Genetic regulatory networks** control development and functioning of organisms



Initiation of sporulation in *Bacillus subtilis*

Qualitative analysis of genetic networks

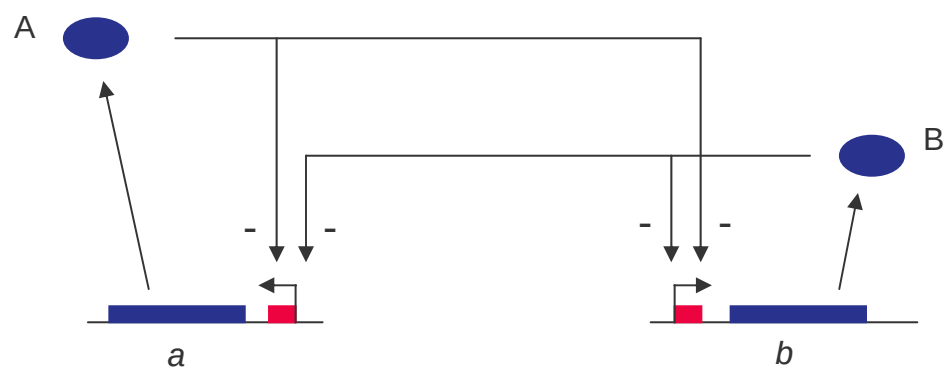
- Genetic regulatory networks are **large** and **complex**
- Computer support indispensable for dynamical analysis of genetic regulatory systems: **modeling** and **simulation**
  - precise and unambiguous description of network
  - systematic derivation of behavior predictions
- **Quantitative information** on kinetic parameters and molecular concentrations usually not available
- Method for **qualitative** simulation of **large** and **complex** genetic regulatory networks *de Jong, Gouzé, et al. (2004), Bull. Math. Biol.*

PL models of genetic regulatory networks

- Genetic networks modeled by class of differential equations using **step functions** to describe regulatory interactions

$$\dot{x}_a = \kappa_a \, s^-(x_a, \theta_{a2}) \, s^-(x_b, \theta_{b1}) - \gamma_a x_a$$
$$\dot{x}_b = \kappa_b \, s^-(x_a, \theta_{a1}) \, s^-(x_b, \theta_{b2}) - \gamma_b x_b$$

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



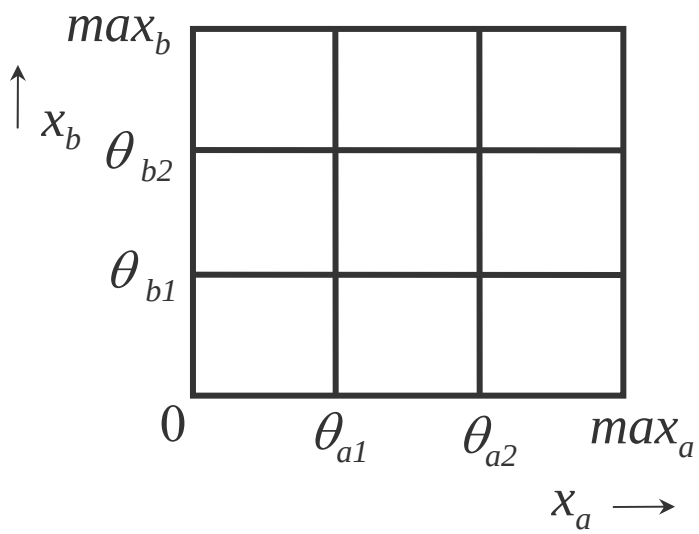
- Differential equation models of regulatory networks are **piecewise-linear (PL)**

Glass, Kauffman (1973), J. Theor. Biol.

Analysis of dynamics in phase space

- Phase space divided into **domains** by threshold planes

  Regulatory and switching domains



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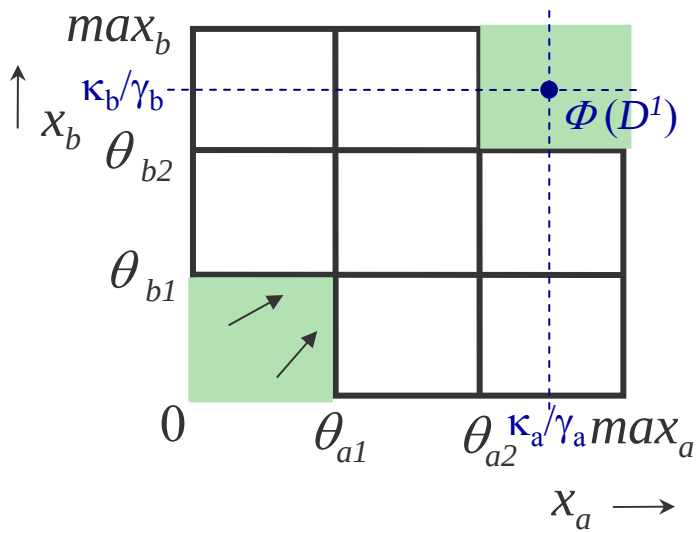
  Regulatory and switching domains

- In every regulatory domain D, system monotonically tends towards **target equilibrium set** $\Phi(D)$



model in D^1 : $\dot{x}_a = \kappa_a - \gamma_a x_a$

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

$$\Phi(D^1) = \{(\kappa_a/\gamma_a, \kappa_b/\gamma_b)\}$$

$$\dot{x}_a = \kappa_a s^-(x_a, \theta_{a2}) s^-(x_b, \theta_{b1}) - \gamma_a x_a$$

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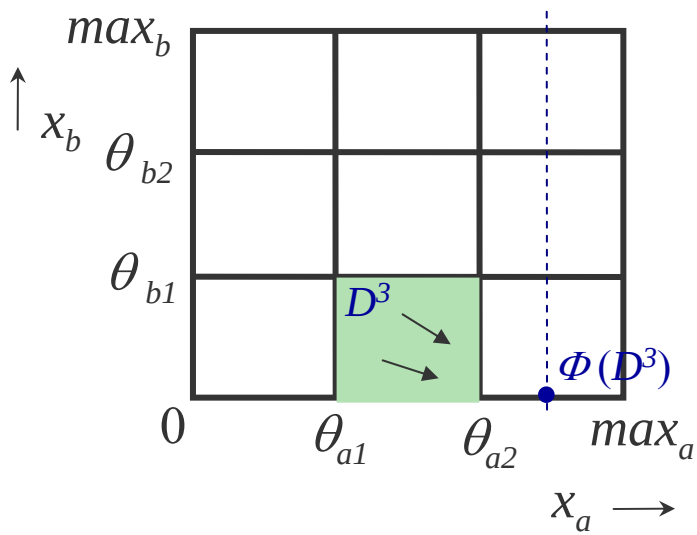

model in D^3 : $\dot{x}_a = \kappa_a - \gamma_a x_a$

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

$$\Phi(D^3) = \{(\kappa_a / \gamma_a, 0)\}$$

$$\dot{x}_a = \kappa_a s^-(x_a, \theta_{a2}) s^-(x_b, \theta_{b1}) - \gamma_a x_a$$

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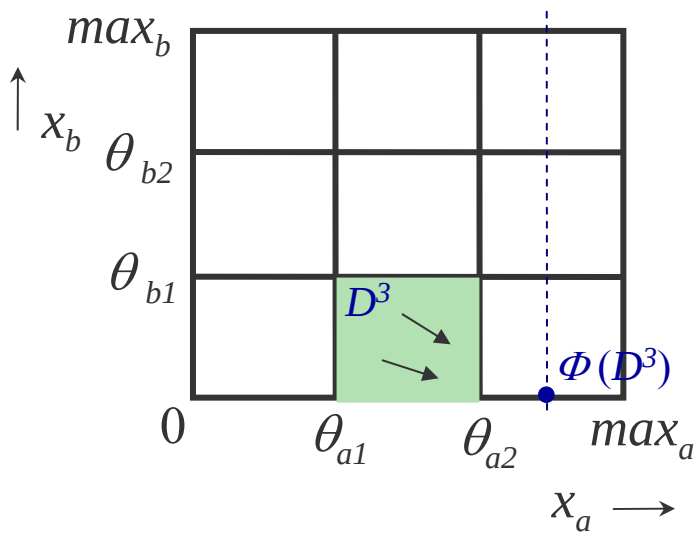

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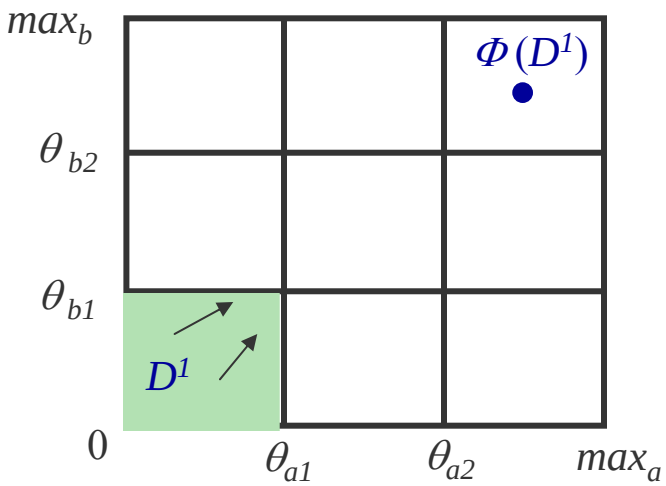
- Use of Filippov generalization to cope with PLDE discontinuities

Gouzé, Sari (2003), Dyn. Syst.

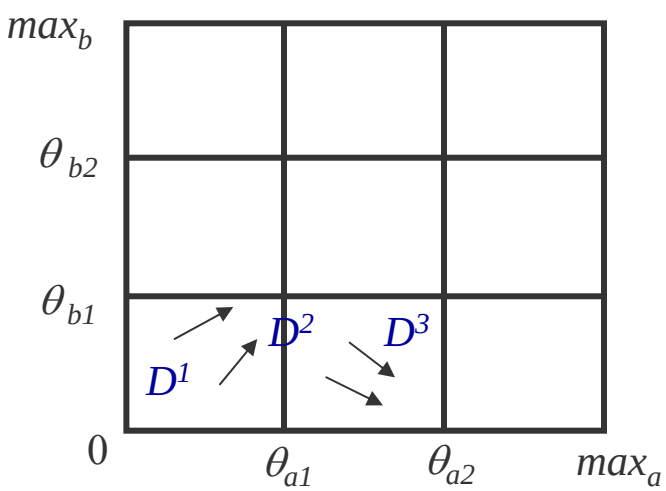
Qualitative description of dynamics

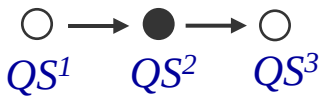


$QS^1 = \langle D^1, \{(1,1)\} \rangle$

- **Qualitative state** consists of domain D and relative position of target equilibrium set $\Phi(D)$

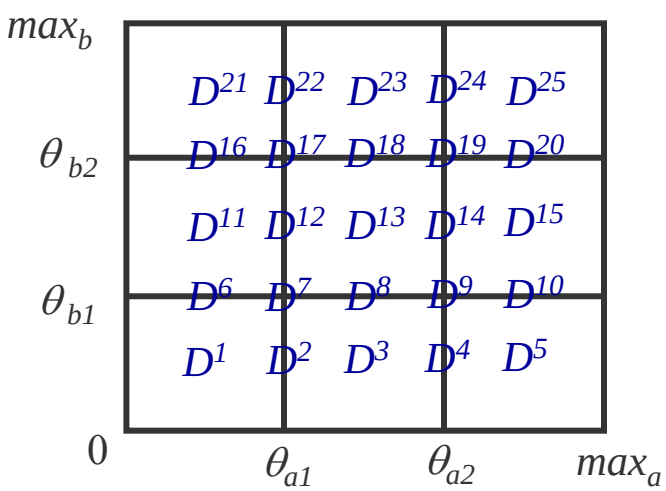
Qualitative description of dynamics

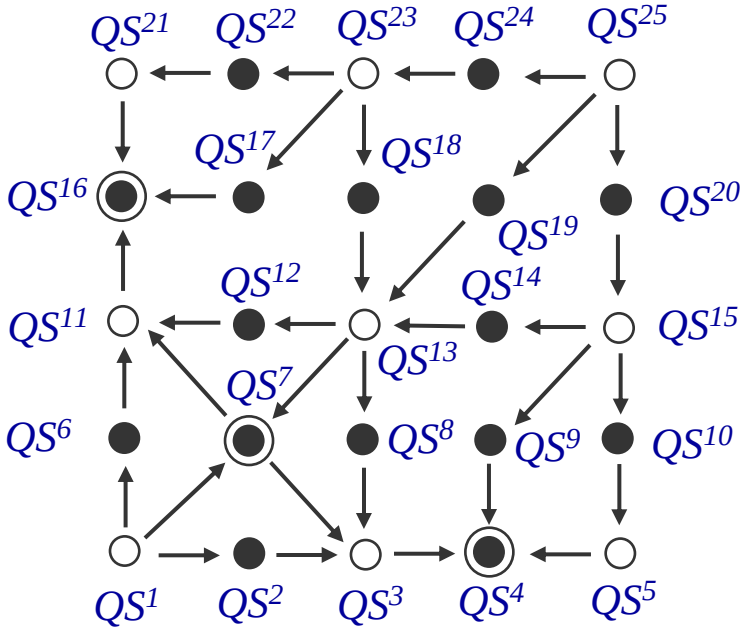




- **Qualitative state** consists of domain D and relative position of target equilibrium set $\Phi(D)$
- **Transition** between qualitative states associated with D and D', if trajectory starting in D reaches D'

Qualitative description of dynamics





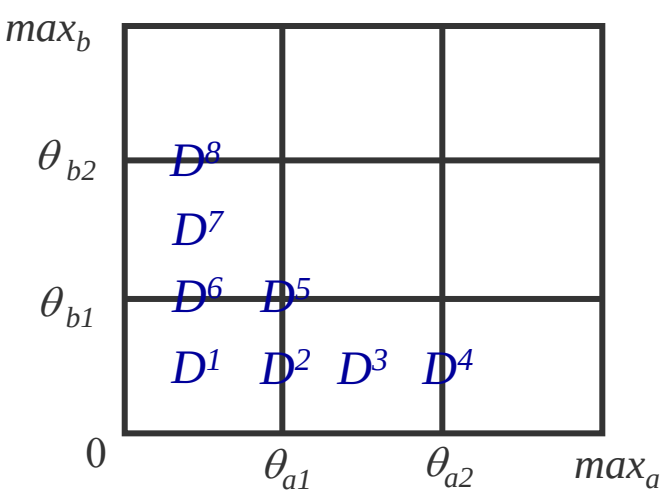
- **Qualitative state** consists of domain D and relative position of target equilibrium set $\Phi(D)$
- **Transition** between qualitative states associated with D and D', if trajectory starting in D reaches D'
- Set of states and transitions results in **state transition graph**

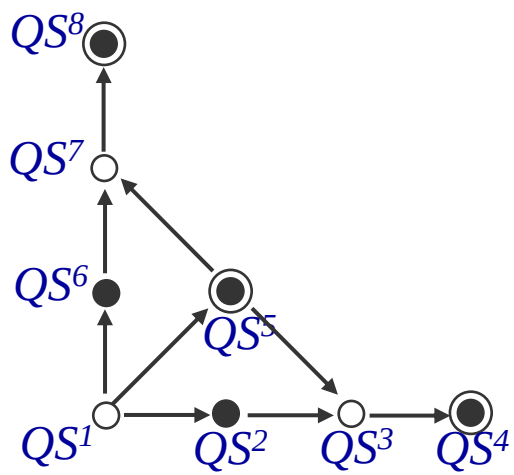
Qualitative simulation

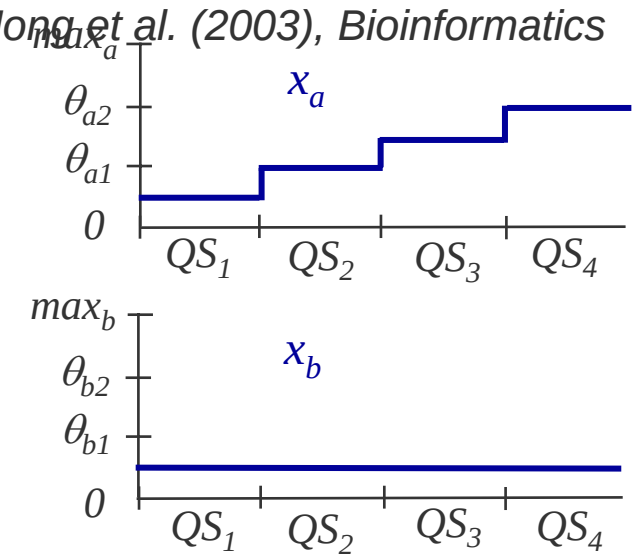
- **Qualitative simulation** determines all qualitative states that are reachable from initial state through successive transitions

Method implemented in Java 1.4: **Genetic Network Analyzer (GNA)**

de Jong et al. (2003), Bioinformatics





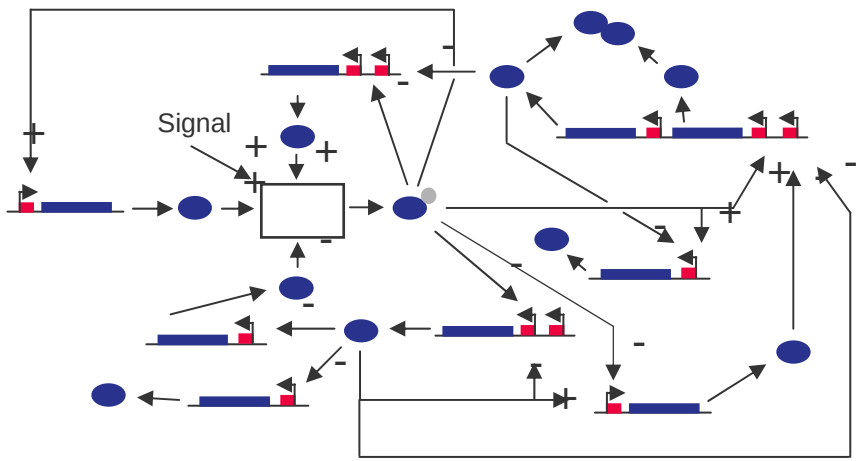


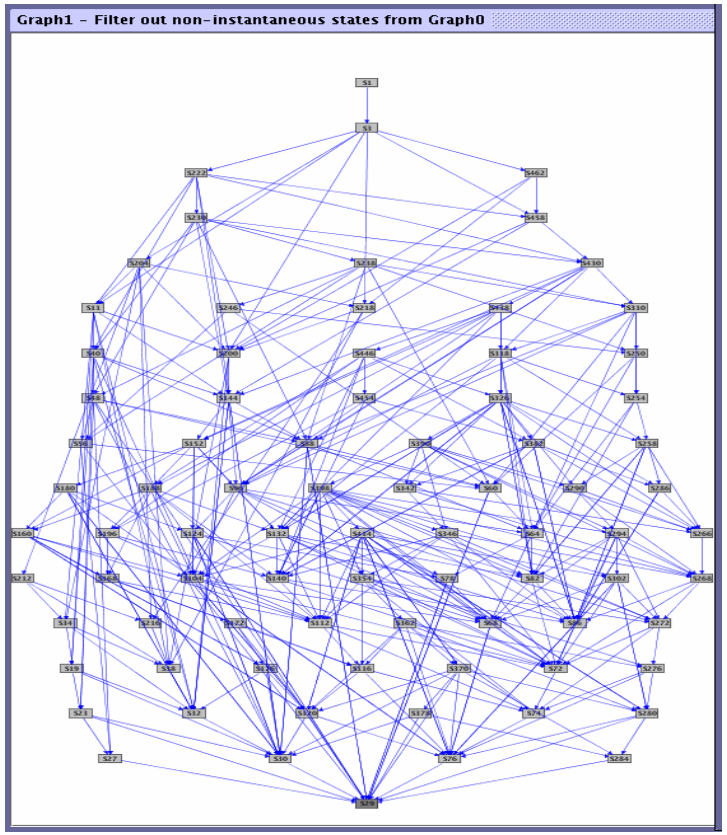
- State transition graph can be used to **test validity** of model using experimental data

Analysis of simulation results

- **Bottleneck** of qualitative simulation: visual inspection of large state transition graphs

Initiation of sporulation in *B. subtilis*





Formal analysis of genetic networks

- **Goal**: develop a method that can test if state transition graph satisfies certain properties

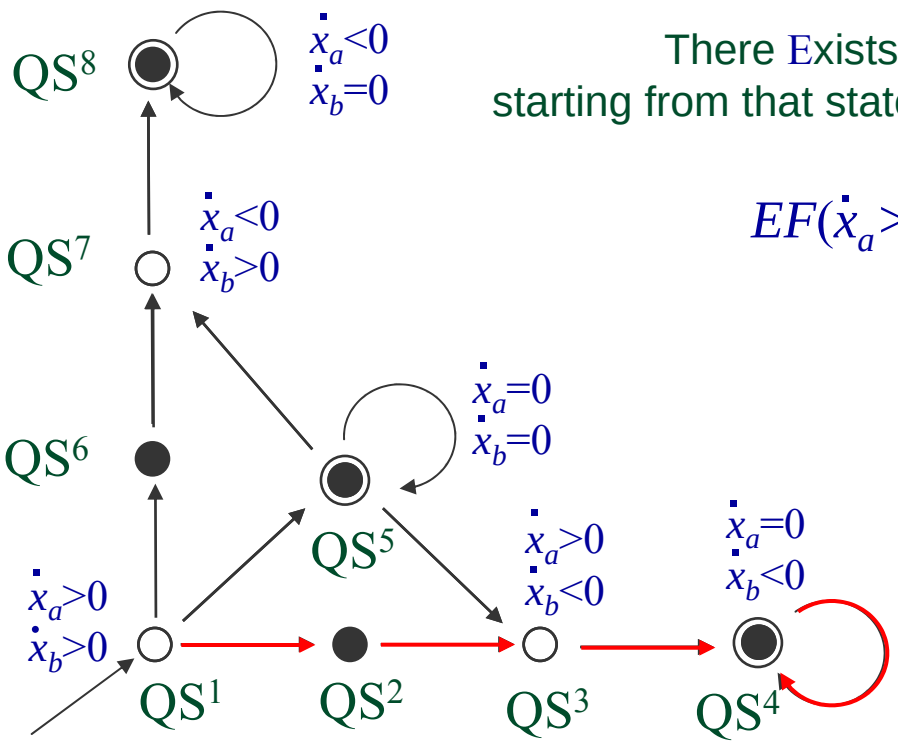
  Is transition graph consistent with observed behavior?

- **Model checking** is automated technique for verifying that finite state system satisfies certain properties

- Computer tools are available to perform automated, efficient and reliable model checking (NuSMV)

Model checking

- Use of model-checking techniques
  - transition graph transformed into **Kripke structure**
  - properties expressed in **temporal logic**



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 $\dot{x}_b<0$

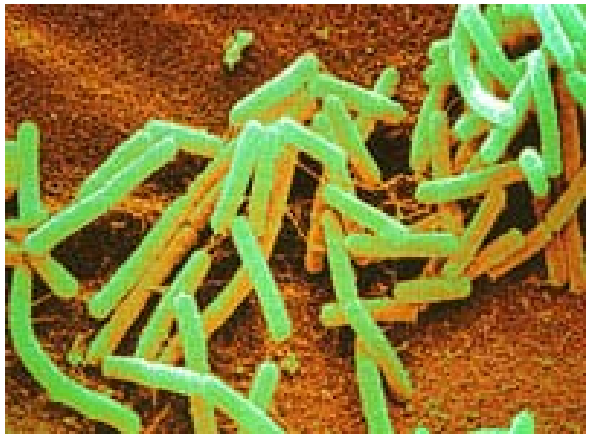
$$EF(\dot{x}_a>0 \wedge \dot{x}_b>0 \wedge EF(\dot{x}_a=0 \wedge \dot{x}_b<0))$$

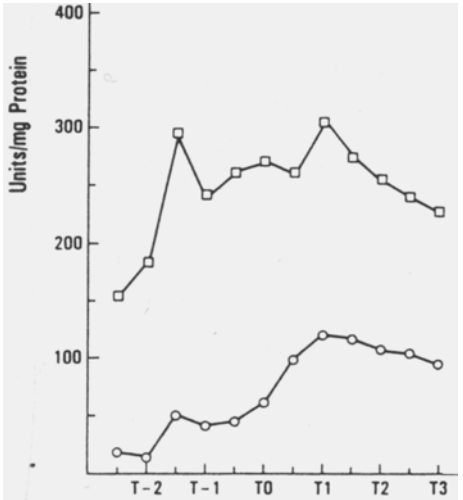
Yes!

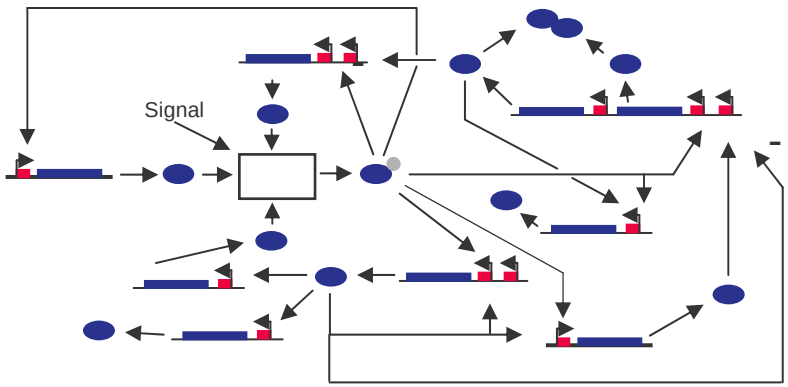
Summary of approach

- Test validity of *B. subtilis* sporulation models

Batt et al. (2004), SPIN04, LNCS







" [The expression of the gene *hpr*] increase in proportion of the growth curve, reached a maximum level at the early stationary phase [(T1)] and remained at the same level during the stationary phase" (Perego and Hoch, 1988)

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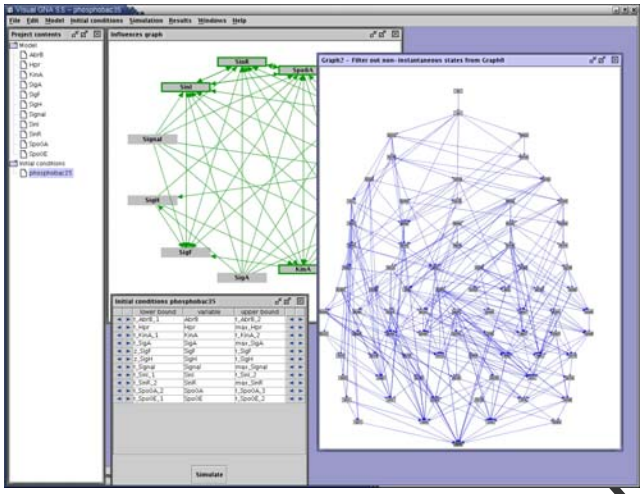

$$EF(\dot{x}_{hpr}>0 \wedge EF\ EG(\dot{x}_{hpr}=0))$$

Kripke structure

temporal logic

model checking

Discussion

- Method towards analysis of genetic regulatory networks based on combination of **qualitative simulation** and **model checking**
- Comparison with existing approaches: tailored method to achieve upscalability
- Initial tests prove in-principle feasibility, realistic application to *E. coli* stress response under way
- Applicability of the approach to biological systems:
  - qualitative modeling and simulation adapted to genetic regulatory networks
  - temporal logic allows biological properties to be formalized

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