Model Checking Genetic Regulatory Networks using GNA and CADP

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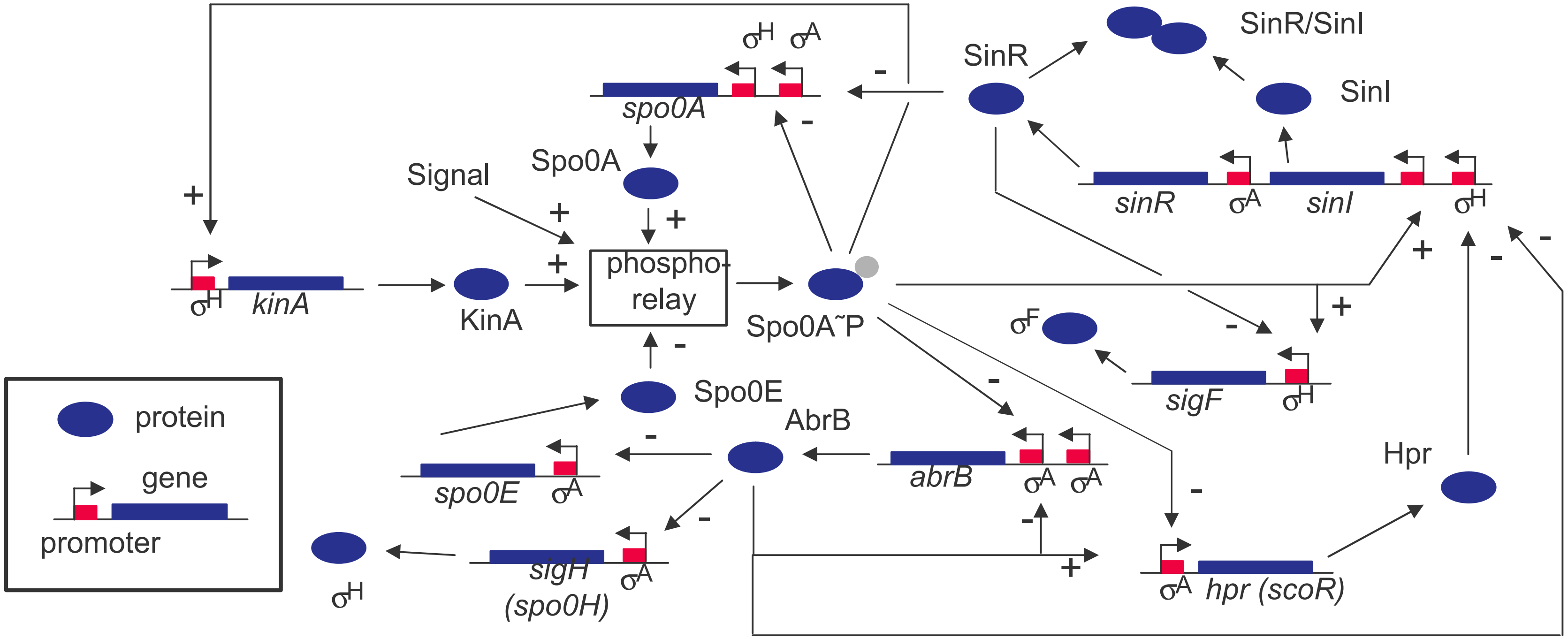
http://www-helix.inrialpes.fr/gna http://www.inrialpes.fr/vasy/cadp

Overview

1. Introduction
2. Qualitative simulation of genetic regulatory networks (GNA)
3. Model checking of genetic regulatory networks (CADP)
4. Demonstration of GNA and CADP
5. Discussion and further work

Genetic regulatory networks

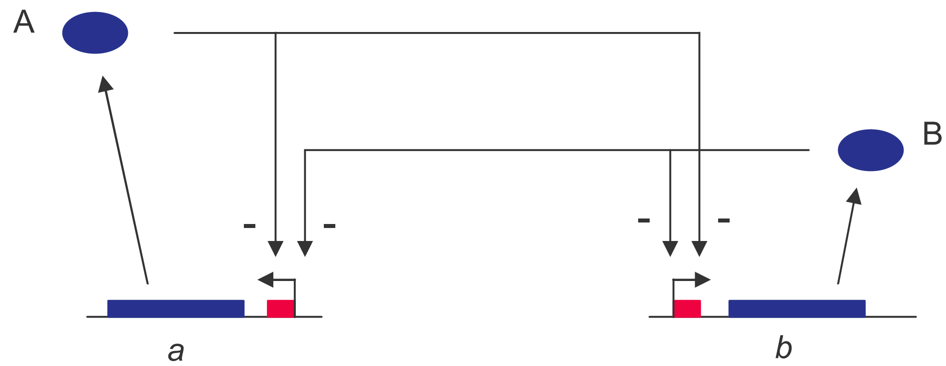
- **Genetic regulatory networks** control development and functioning of organisms



Initiation of sporulation in *Bacillus subtilis*

PL models of genetic regulatory networks

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

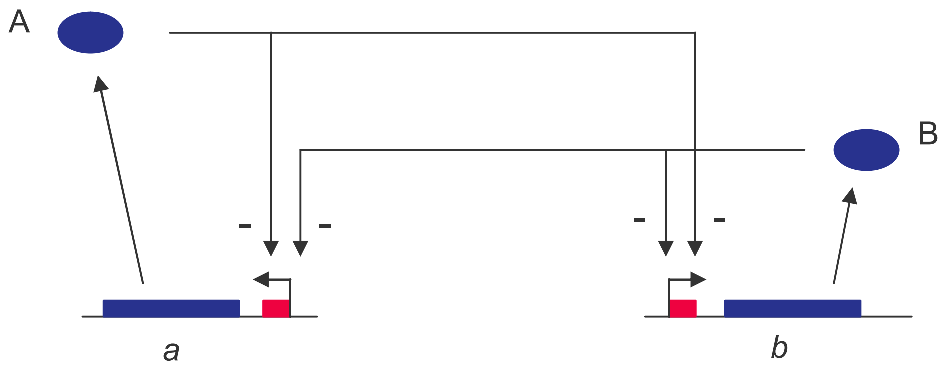


PL models of genetic regulatory networks

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

$$\dot{x}_a = k_a\, s^-(x_a, q_{a2})\, s^-(x_b, q_{b1}) - g_a\, x_a$$

$$\dot{x}_b = k_b\, s^-(x_a, q_{a1})\, s^-(x_b, q_{b2}) - g_b\, x_b$$



x : protein concentration

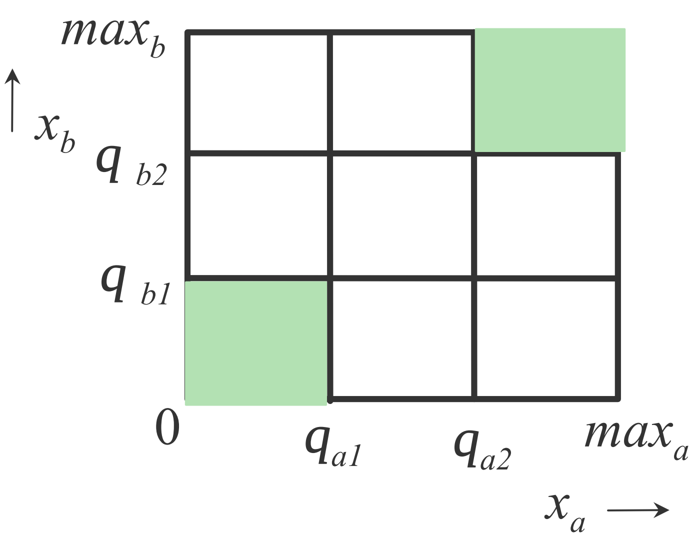
q : threshold concentration

k , g : rate constants

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

Analysis of dynamics in phase space

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



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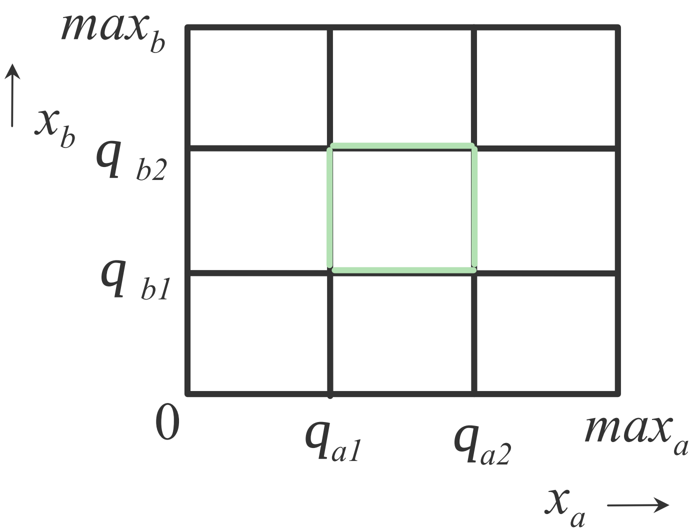

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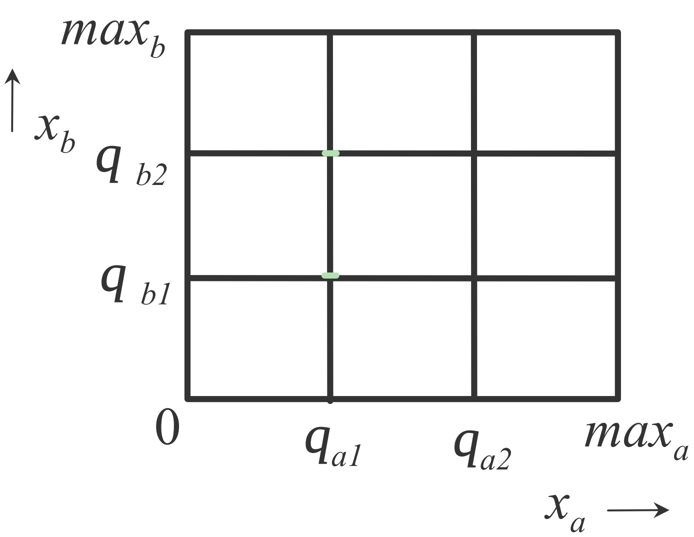

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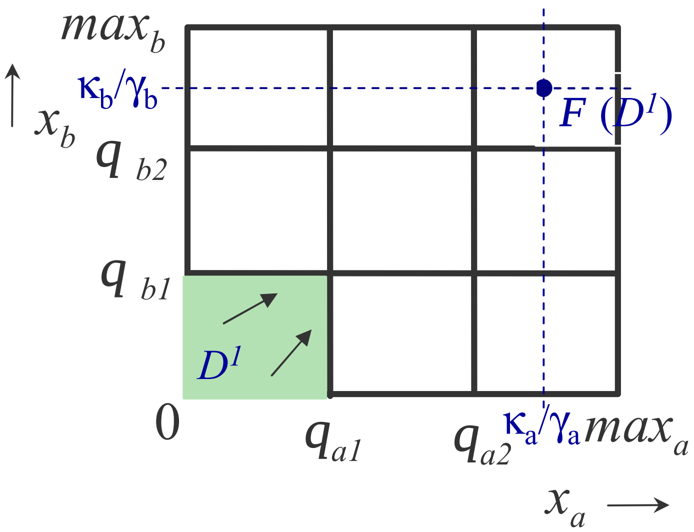
Analysis of dynamics in phase space

- Phase space divided into **domains** by threshold planes
- In every domain D, system monotonically tends towards **target equilibrium set** $F\ (D)$

Persistent and instantaneous domains



model in D^1 :
$$\dot{x}_a = k_a - g_a\, x_a$$
$$\dot{x}_b = k_b - g_b\, x_b$$

$$F\ (D^1) = \{(k_a\,/g_a\,,\ k_b\,/g_b\,)\}$$

$$\dot{x}_a = k_a\, s^-(x_a\,,\ q_{a2})\ s^-(x_b\,,\ q_{b1}\,) - g_a\, x_a$$
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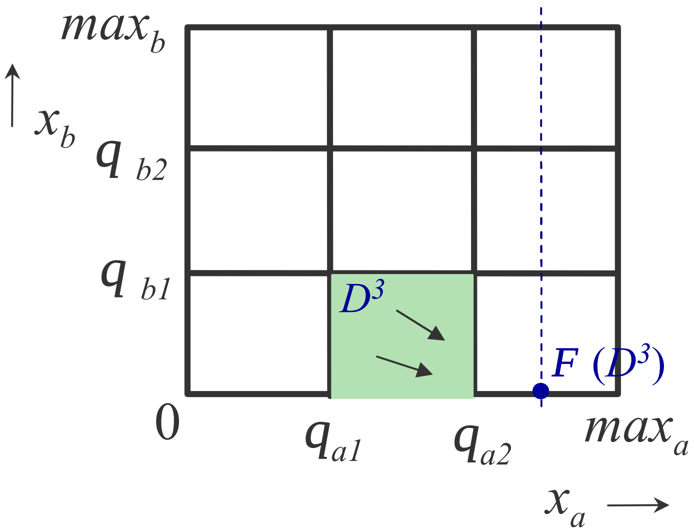

model in D^3 : $\dot{x}_a = k_a - g_a\, x_a$

$$\dot{x}_b = -\, g_b\, x_b$$

$$F\ (D^3) = \{(k_a / g_a\ , 0\ )\}$$

$$\dot{x}_a = k_a\, s^-(x_a\, , q_{a2})\, s^-(x_b\, , q_{b1}) - g_a\, x_a$$

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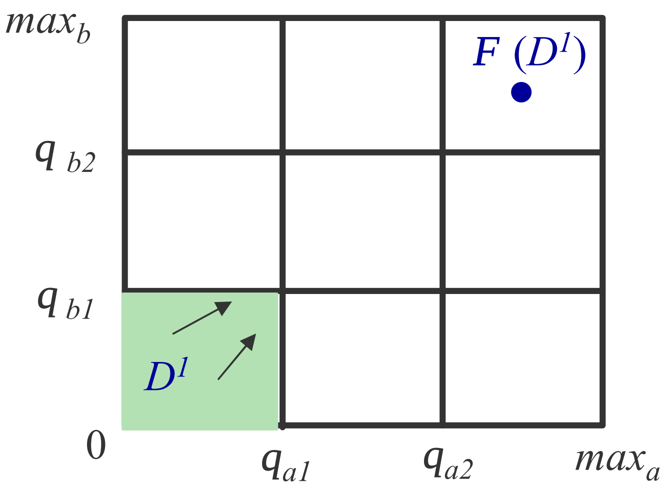
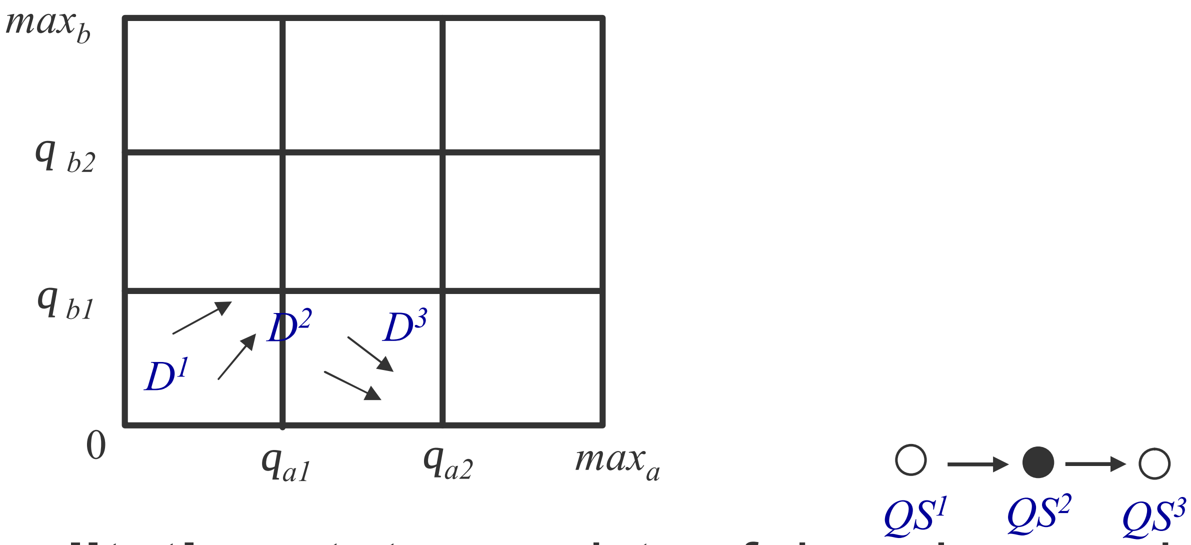
Qualitative description of dynamics



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

❖ **Qualitative state** consists of domain D and the derivative signs of solutions in D, $\boldsymbol{S}$: $QS = < D, \boldsymbol{S} >$

Qualitative description of dynamics



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- **Transition** between qualitative states associated with D and D', if trajectory starting in D reaches D'

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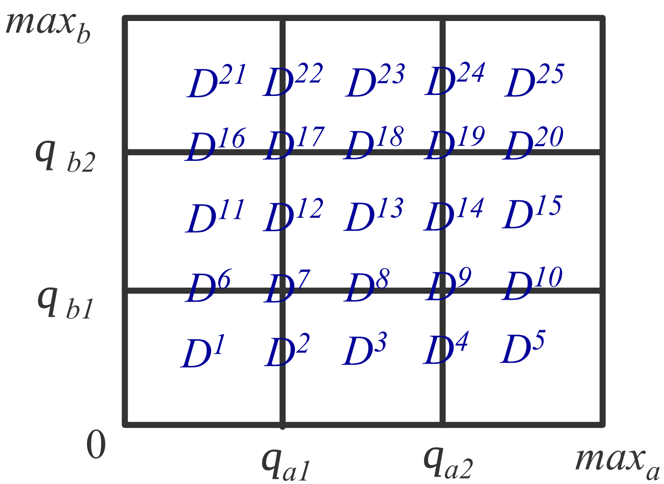
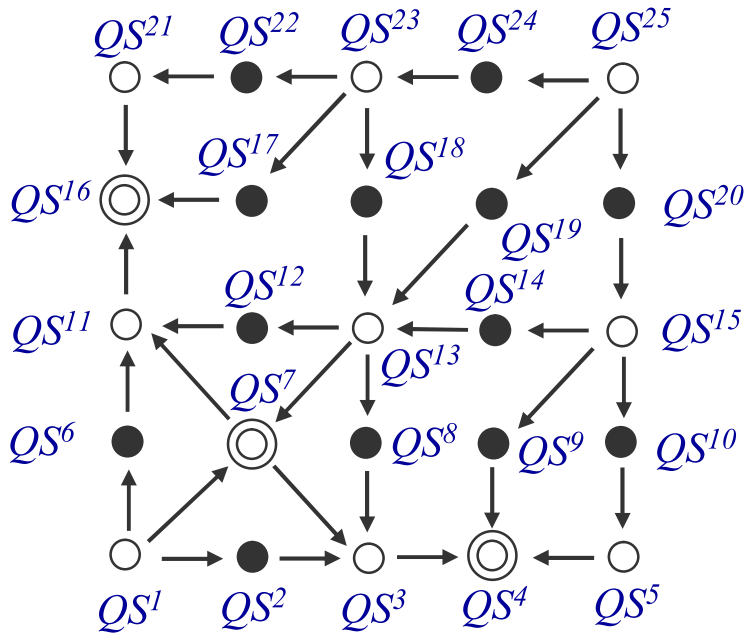


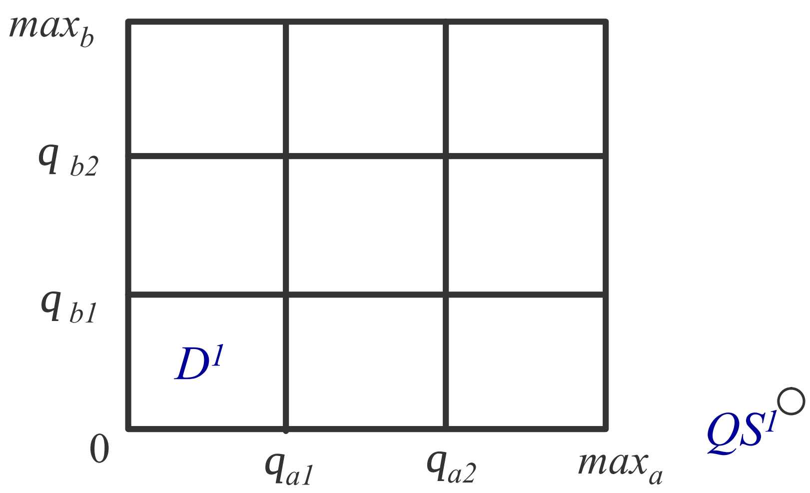


- **Qualitative state** consists of domain D and the derivative signs of solutions in D, $\boldsymbol{S}$: $QS = < D, \boldsymbol{S} >$
- **Transition** between qualitative states associated with D and D', if trajectory starting in D reaches D'
- Set of states and transitions results in **state transition graph**

Qualitative simulation

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

  Simulation method implemented in **Genetic Network Analyzer (GNA)**



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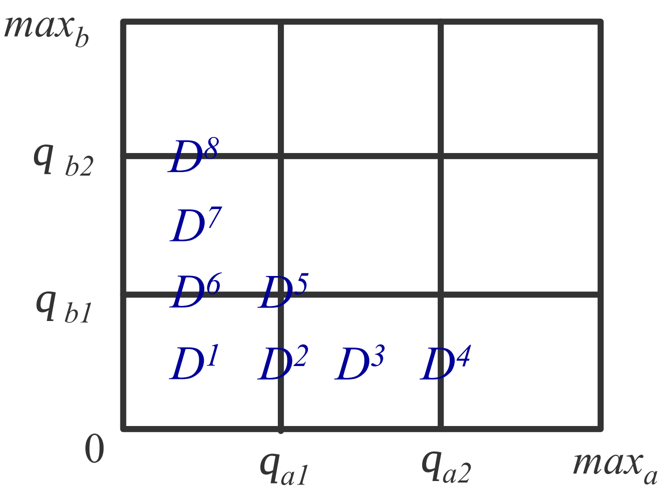

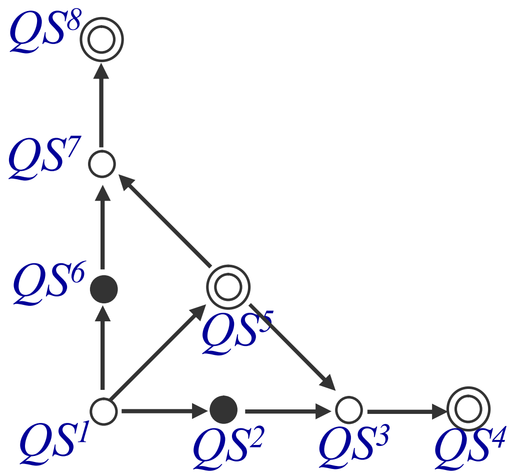

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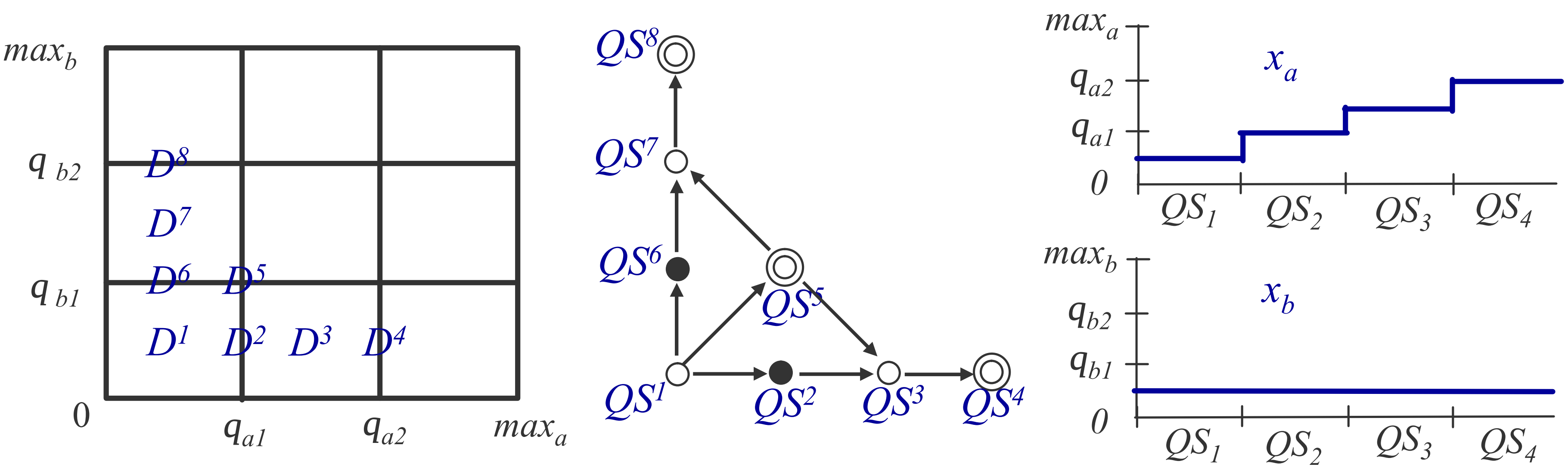


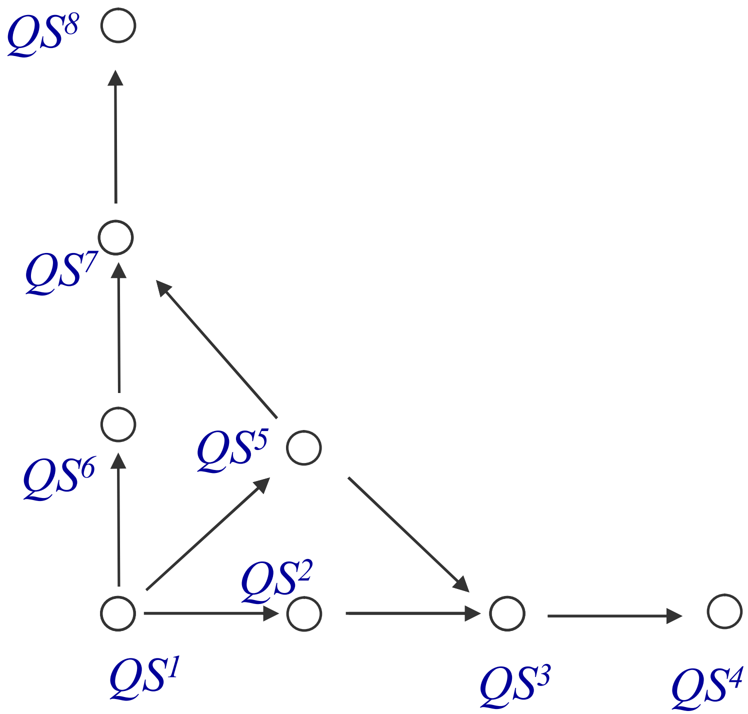
- State transition graph can be used to explore properties of network

CADP tool box

- Input languages
  - ISO formal description techniques (LOTOS)
  - Explicit LTSs (BCG) or networks of communicating LTSs (EXP, FC2)
- Functionalities
  - Compilation, rapid prototyping
  - Interactive and guided simulation
  - Equivalence checking and model checking
  - Compositional and on-the-fly verification
  - Test generation
- Applications
  - 74 case-studies, 17 research tools

Model checking simulation results

- Transition graph transformed into **labeled transition system**



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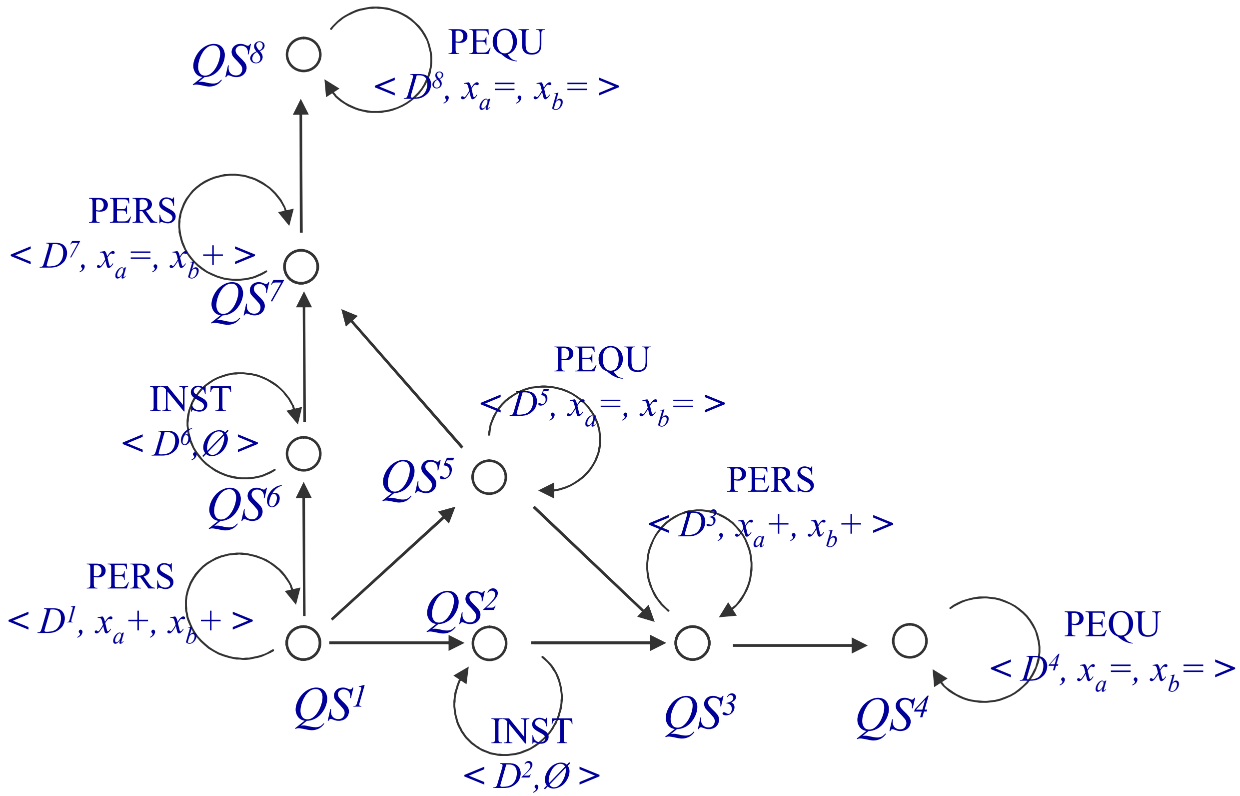

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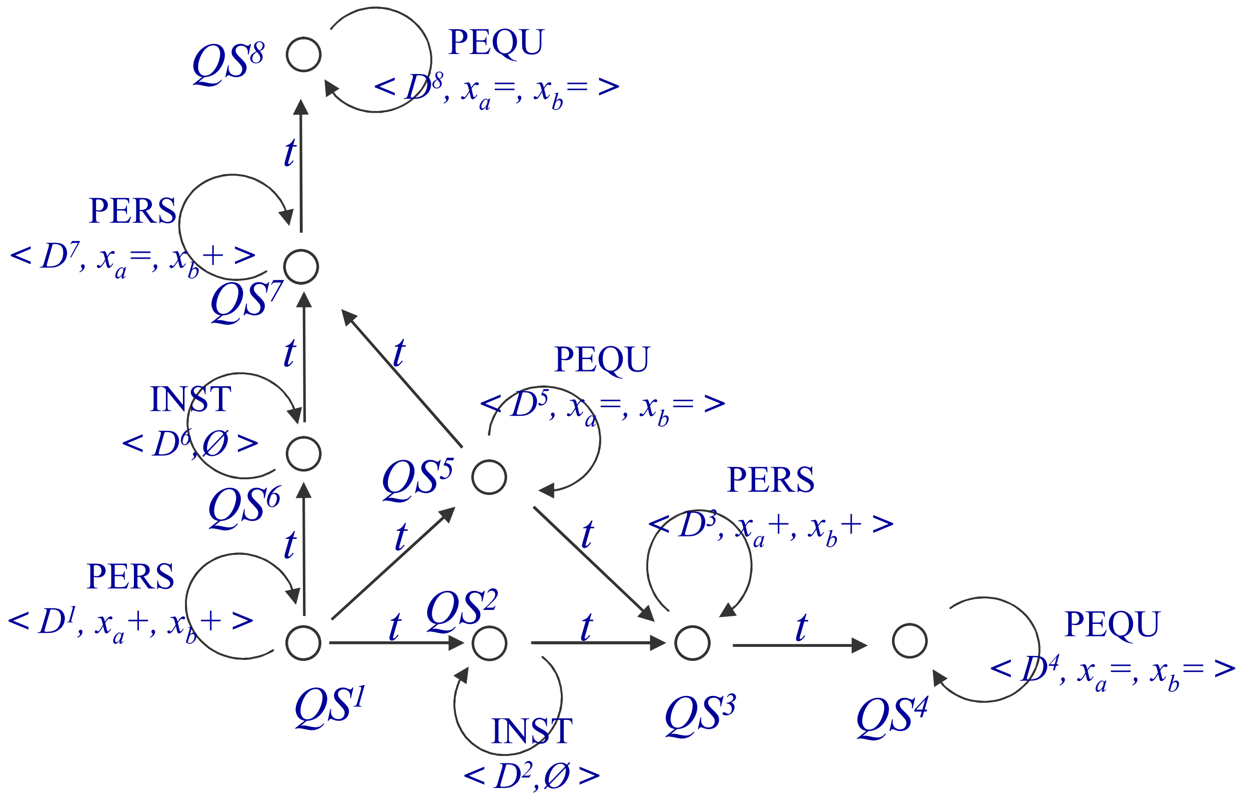

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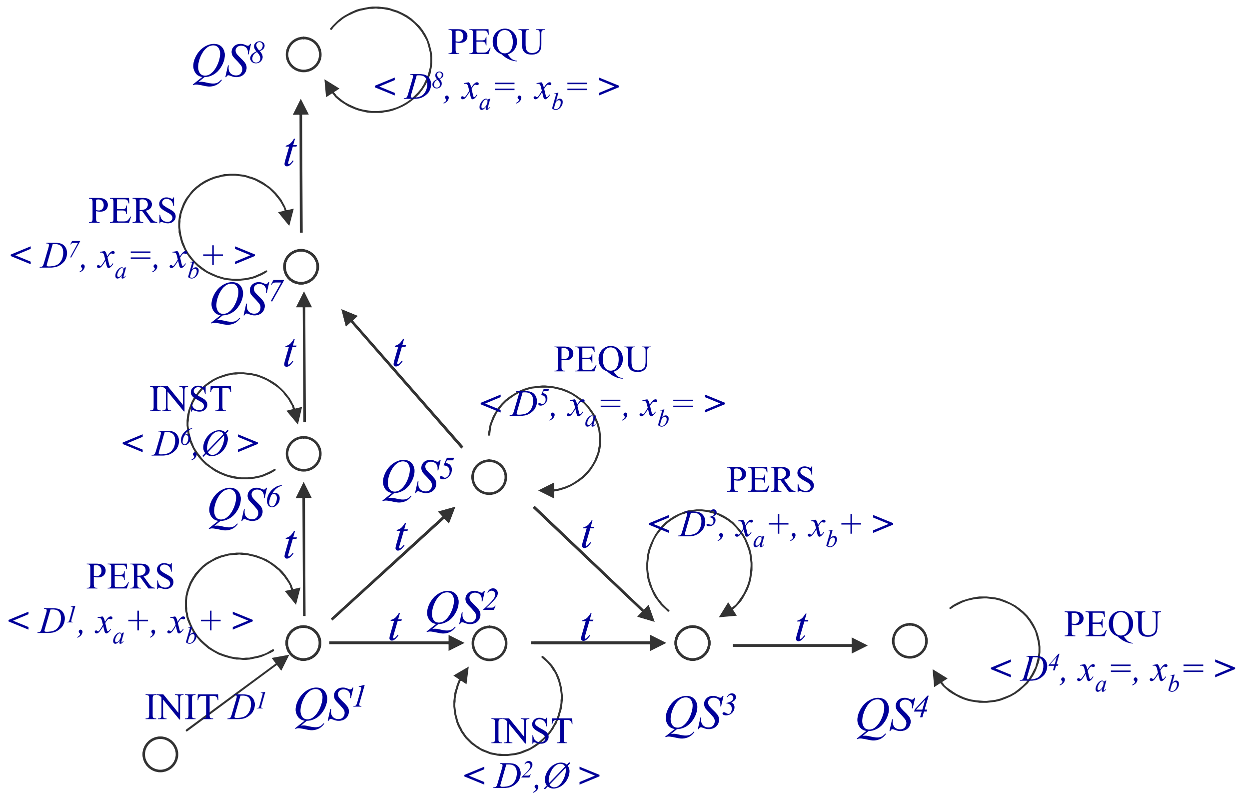

- Tool used: GNA2BCG

Model checking simulation results

- LTS reduction and analysis using bisimulations

  Instantaneous states abstracted away by branching bisimulation

- Diagnostic of properties in regular alternation-free μ-calculus

  Action predicates, regular expressions over transition sequences, boolean, modal and fixed point operators

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bistability property

$$[\ \text{“}\mathit{INIT}\ D^{1}\text{”}\ ]\ (\ <\ \mathit{true}^{*}\ .\ \text{“}\mathit{PEQU}\ D^{4}\ A{=}\ B{=}\text{”}\ >\ \mathit{true}\ \ \mathit{and}\ \ <\ \mathit{true}^{*}\ .\ \text{“}\mathit{PEQU}\ D^{8}\ A{=}\ B{=}\text{”}\ >\ \mathit{true}\ )$$

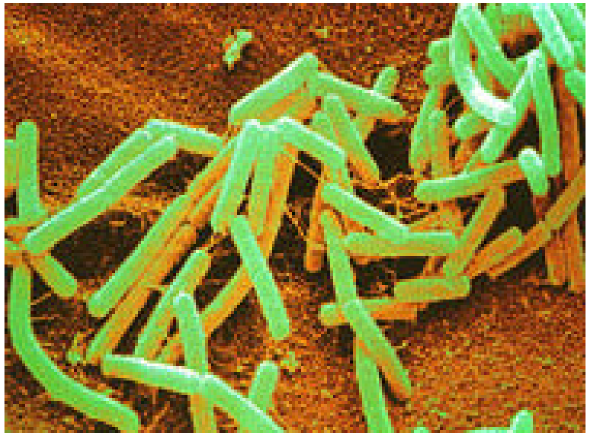
- Tools used: ALDEBARAN and EVALUATOR 3.0

Demonstration: GNA and CADP

- State transition graph generated using Genetic Network Analyzer
- State transition graph exported as labelled transition system, in BCG format
- Labelled transition system analyzed using CADP

Summary of approach

- Test validity of *B. subtilis* sporulation models



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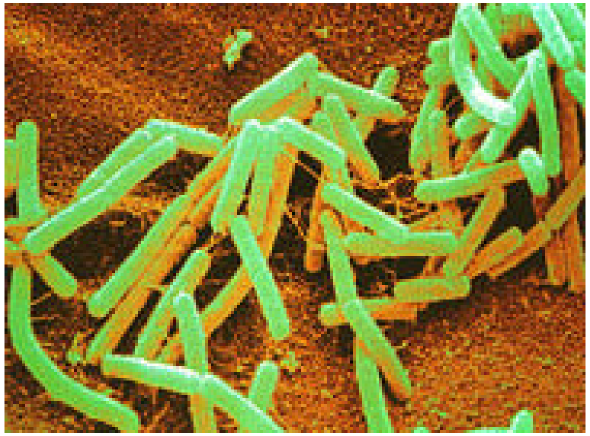

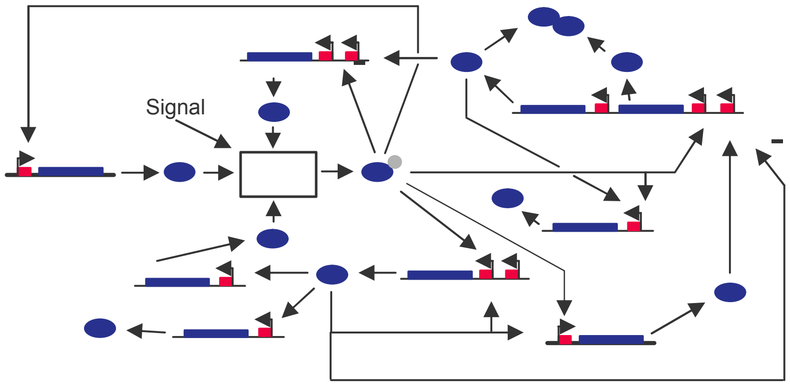

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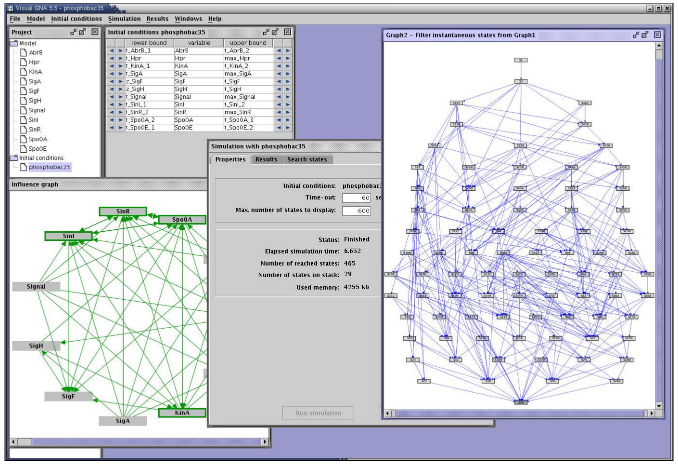

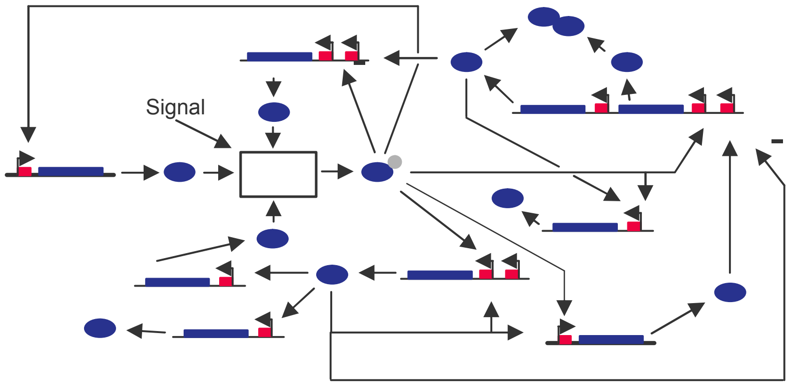

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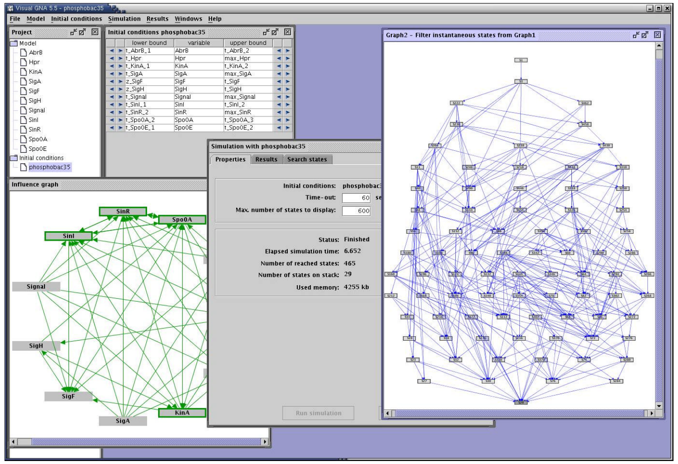

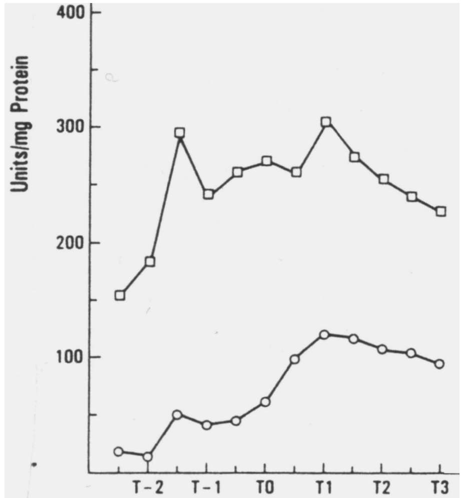

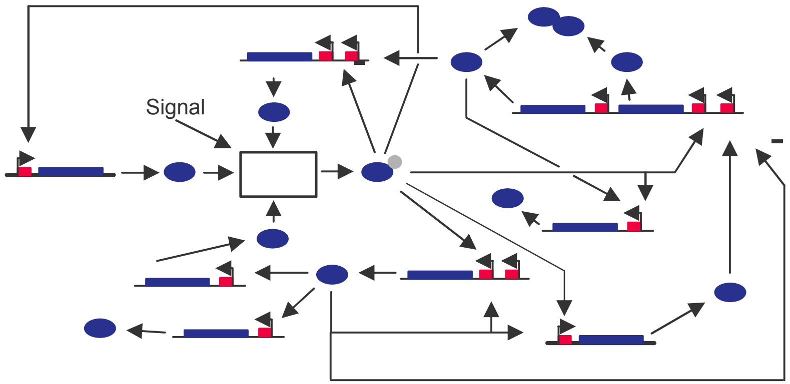

" [The expression of the gene *hpr*] increase in proportion of the growth curve, reached a maximum level at the early stationary phase [(T1)] and remained at the same level during the stationary phase" (Perego and Hoch, 1988)

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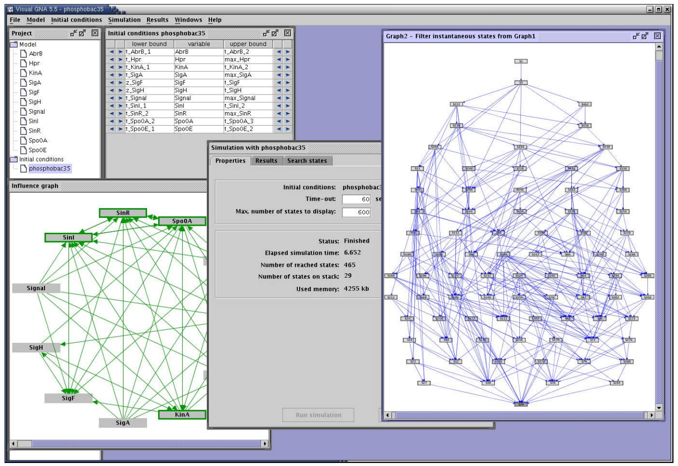
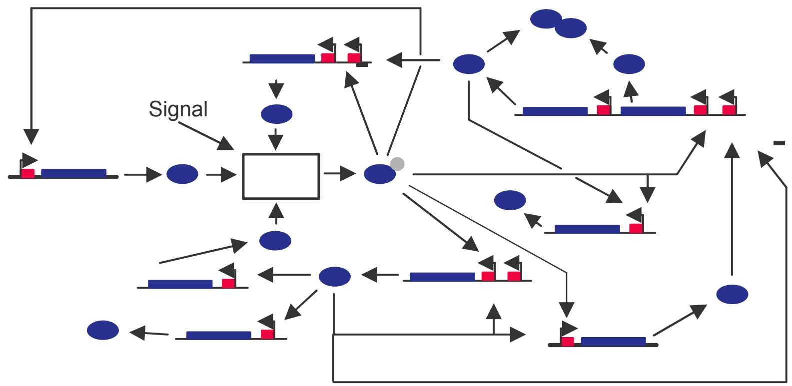
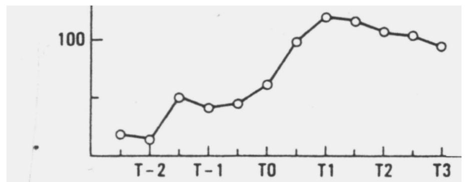




< *true* . ‘.*.Hpr+.*’ . *true* . ‘.*.Hpr=.*’ > *true*



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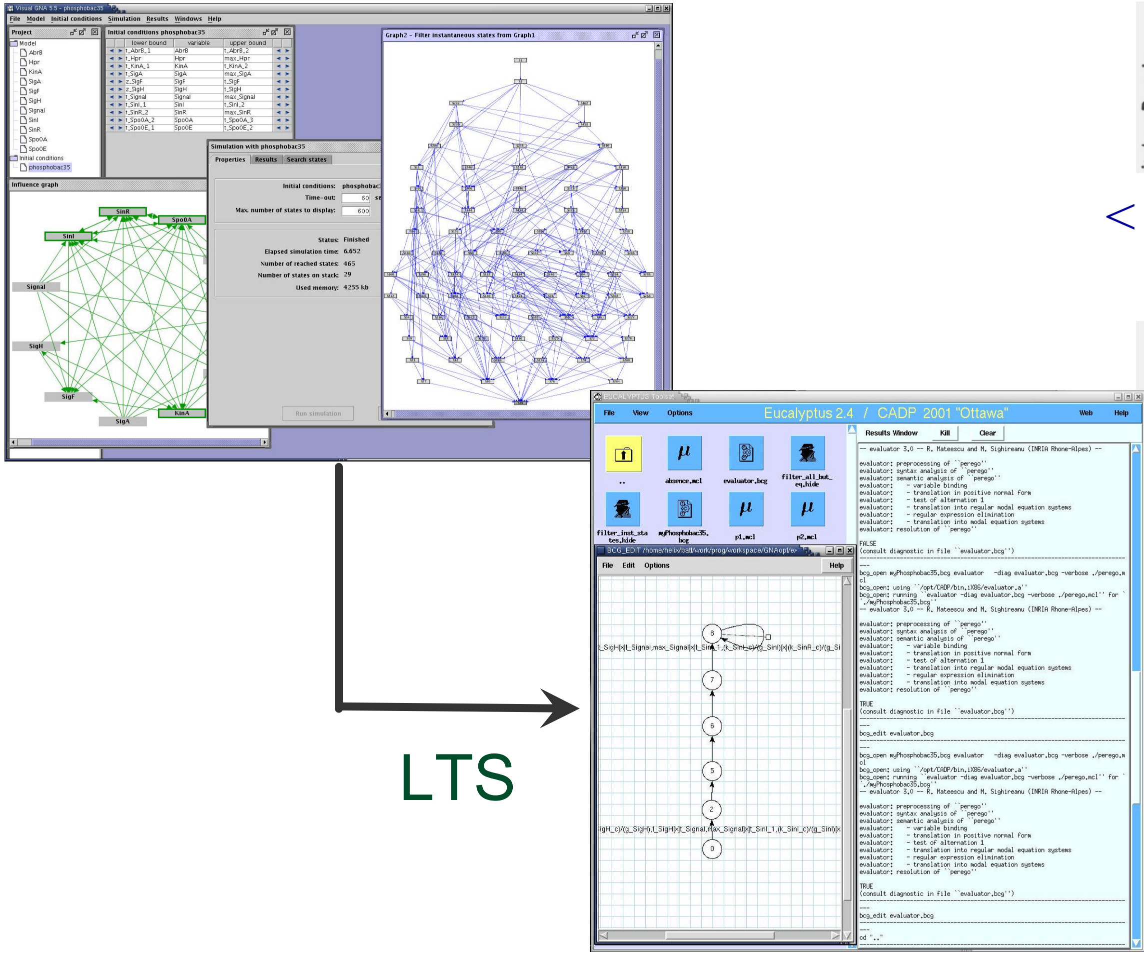
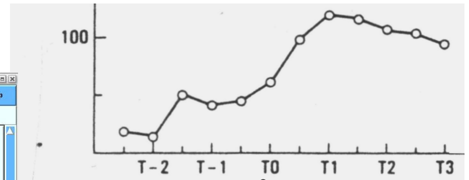


LTS

< *true** . '.*.Hpr+.*' .
*true** . '.*.Hpr=.*' > *true*



μ-calculus

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Related and further work

- Comparison with existing approaches: tailored method to achieve upscalability and applicability
- Further integration between GNA and CADP
- Study of property classes adapted to analysis of GRNs
  - Property classes related to transient and steady-state behavior of cell
  - Behavioral equivalence of networks in different genetic contexts or organisms
- Application to more complex and less-understood GRNs

  Study of nutritional stress response of *Escherichia coli*

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