# Temporal Logic Patterns for Querying Qualitative Models of Genetic Regulatory Networks

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# Outline


1. *Introduction*
   - Motivation: qualitative simulation of large genetic regulatory networks
   - Computational approach: formal verification

2. *Query patterns for formal verification*
   - Definition of patterns: why patterns?
   - Proposed patterns
   - Translation to temporal logic

3. *Analysis of the carbon starvation response in E.coli*
   - Carbon starvation response model
   - Analysis using query patterns

4. *Conclusions and perspectives*

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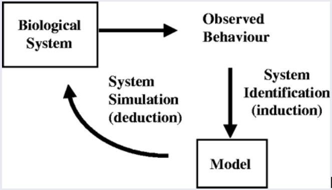
# Motivation

## Qualitative simulation of dynamical systems

Some real world problems lack quantitative information (Kuipers, 1994)

## Biological systems

Study of the interactions between molecular components, and how these interactions give rise to the function and behavior of those systems




King, Garrett and Coghill, 2005

# Motivation

## Use of qualitative models to analyze genetic regulatory networks

- Understanding how particular molecular mechanisms control a cellular process
- Predicting novel phenomena that can be confronted with experimental data

## Examples of qualitative models in biology

- Regulation of arginine anabolism (Thomas et al., 1995)
- Intracellular thiamine kinetics in the intestine tissue (Bellazzi et al., 2001)
- Simulation of Glycolysis (King et al., 2005)
- ...

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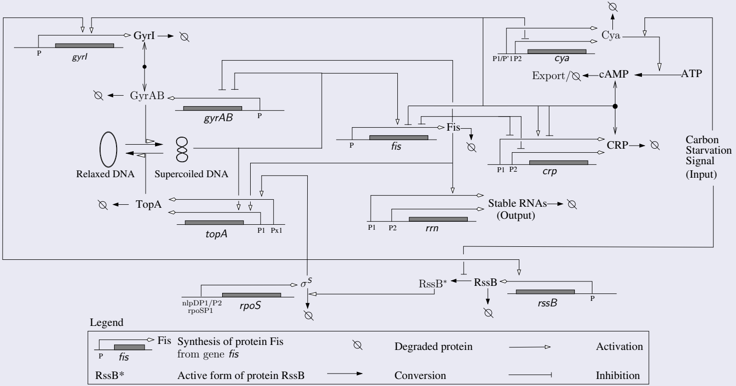
# Motivation

## The network of global regulators in *E. coli*




## Problem

Explosion of the number of qualitative behaviors when dealing with large and complex networks

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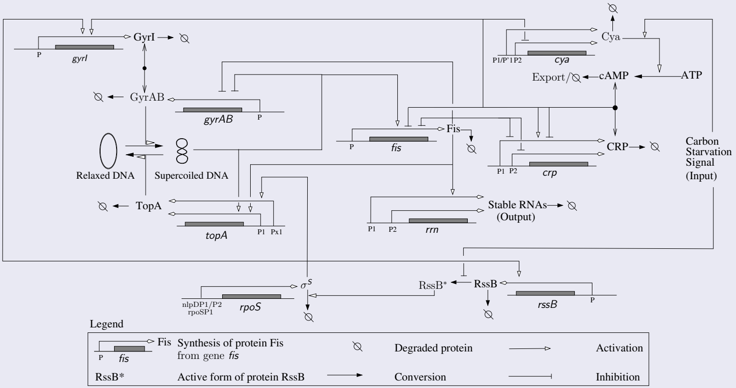
## The network of global regulators in E. coli

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Explosion of the number of qualitative behaviors when dealing with large and complex networks

# Computational approach

## Use of formal verification techniques

Formal verification based on temporal logic and model checking provides a powerful technology for the analysis of qualitative models (Shults and Kuipers, 1997)

## Existing examples of model checking of qualitative models in biology

- Mucus production in *P. aeruginosa*, Bernot et al. (2004)
- Carbon starvation response in *E.coli*, Batt et al. (2005)
- ERK intracellular signalling pathway, Calder et al. (2005)

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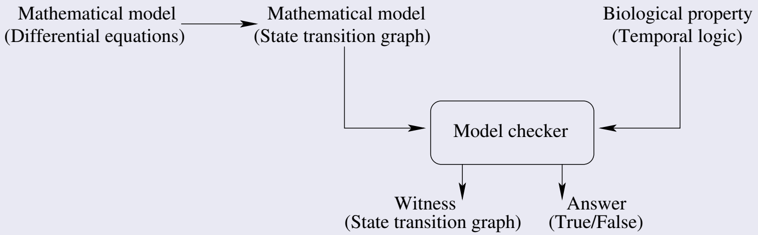

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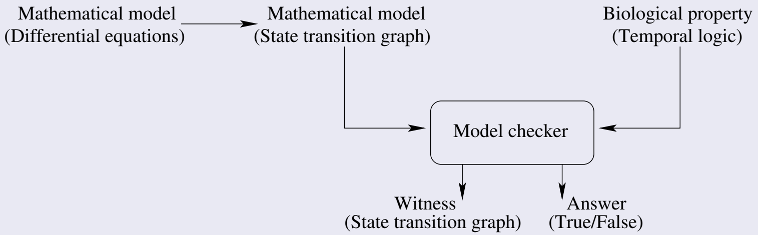
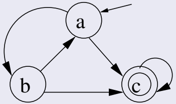



## Example of model checking

State transition graph




Temporal logic property

$a \wedge EF(b \wedge EF(c \ U \ a))$

# Computational approach

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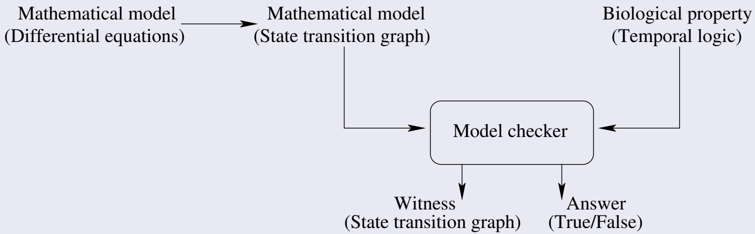


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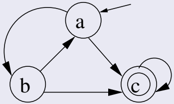


Temporal logic property
$a \wedge EF(b \wedge EF(c\ U\ a))$

Response: False!

# Computational approach

## Problem

- How to pose relevant questions when analyzing a large network model?
- Not easy for non-experts to formulate queries in temporal logic

## Example of a temporal logic query

$EF(\phi_g) \wedge \neg E(\text{TRUE}\ U\ (\neg([P] > 0.9\ \mu M) \wedge E(\text{TRUE}\ U\ \phi_g)))$

## Proposed solution

Definition of a pattern system capable of:

- Capturing frequently-asked questions by modelers
- Automatic translation to several temporal logics

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# Patterns

## Pattern definition

Generalized description of commonly occurring questions in a specific application domain

## Why patterns?

- Generic enough to cover most frequently-asked questions
- Assist the user in the query formulation process
- Natural language templates that can be translated into temporal logic

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## Formal verification community

- In 1991, Manna and Pnueli introduced classes of properties that are most frequently verified
- In 1999, Dwyer et al. specified a pattern system to capture recurring questions in a specific application domain

## Application to qualitative reasoning

But: a systematic definition of temporal logic query patterns has not received any attention in qualitative reasoning thus far

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# Pattern identification process

## Patterns should have three main characteristics

- Sufficiently generic
- Sufficiently concrete to be comprehensible
- Minimal overlap

## Biological questions

Collection of relevant biological questions from the literature

## Pattern building

- Grouping of questions into categories: *occurrence/exclusion*, *consequence*, *sequence* and *invariance* of cellular events
- Formulation of patterns for each category that capture essential questions and most relevant variants

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# Occurrence/Exclusion pattern

## Definition: Occurrence/Exclusion pattern

| | | | | |
|---|---|---|---|---|
| It | is possible | for a state | $\phi$ | to occur |
| | is not possible | | | |

## Biological examples

- "It is possible for a state with a high concentration of protein $P_1$ to occur"
- "It is not possible for a state in which protein $P_1$ and protein $P_2$ are highly expressed to occur"

## Consequence pattern

### Definition: Consequence pattern

| | | | | | | |
|---|---|---|---|---|---|---|
| If a state | $\phi$ | occurs, | then it is | possibly | followed by a state | $\psi$ |
| | | | | necessarily | | |

### Biological examples

- "If a state in which a protein $P$ is phosphorylated occurs, then it is possibly followed by a state in which the expression of gene $g$ decreases"
- "If a state in which the concentration of protein $P$ is bellow 5 $\mu M$ occurs, then it is necessarily followed by a state in which the expression of gene $g$ is at the basal level"

# Sequence pattern

## Definition: Sequence pattern

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| A state | $\psi$ | is reachable and is | possibly | preceded | at some time | by a state | $\phi$ |
| | | | necessarily | | all the time | | |

## Biological examples

- "A state in which reactions $R_1$ and $R_2$ occur at a high rate is reachable after 2 min, and is possibly preceded at some time by a state in which the transcription factor $P$ is phosphorylated"
- "A steady state is reachable and is necessarily preceded all the time by a state in which nutrient $N$ is absent"

# Invariance pattern

## Definition: Invariance pattern

| | | | |
|---|---|---|---|
| A state | $\phi$ | can | persist indefinitely |
| | | must | |

## Biological examples

- "A state in which reaction $R$ occurs at a high rate can persist indefinitely"
- "A state with a basal expression of gene $g$ must persist indefinitely"

# Translation to temporal logics

## Translation to CTL

| Occurrence/Exclusion pattern | CTL |
|---|---|
| It **is possible** for a state $\phi$ to occur | $EF\ (\phi)$ |
| It **is not possible** for a state $\phi$ to occur | $\neg EF\ (\phi)$ |
| **Consequence pattern** | |
| If a state $\phi$ occurs, then it is **possibly** followed by a state $\psi$ | $AG\ (\phi \Rightarrow EF\ (\psi))$ |
| If a state $\phi$ occurs, then it is **necessarily** followed by a state $\psi$ | $AG\ (\phi \Rightarrow AF\ (\psi))$ |
| **Sequence pattern** | |
| A state $\psi$ is reachable and is **possibly** preceded **at some time** by a state $\phi$ | $EF\ (\phi \wedge EF\ (\psi))$ |
| A state $\psi$ is reachable and is **possibly** preceded **all the time** by a state $\phi$ | $E\ (\phi\ U\ \psi)$ |
| A state $\psi$ is reachable and is **necessarily** preceded **at some time** by a state $\phi$ | $EF\ (\psi) \wedge \neg E\ (\neg\phi\ U\ \psi)$ |
| A state $\psi$ is reachable and is **necessarily** preceded **all the time** by a state $\phi$ | $EF\ (\psi) \wedge \neg E(\top\ U\ (\neg\phi \wedge E(\top\ U\ \psi)))$ |
| **Invariance pattern** | |
| A state $\phi$ **can** persist indefinitely | $EG\ (\phi)$ |
| A state $\phi$ **must** persist indefinitely | $AG\ (\phi)$ |

## Translation to other temporal logics

CTRL (Mateescu *et al.* 2008) and $\mu$-calculus (Kupferman *et al.* 2000)

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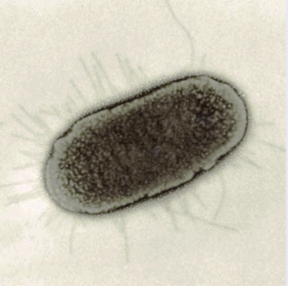
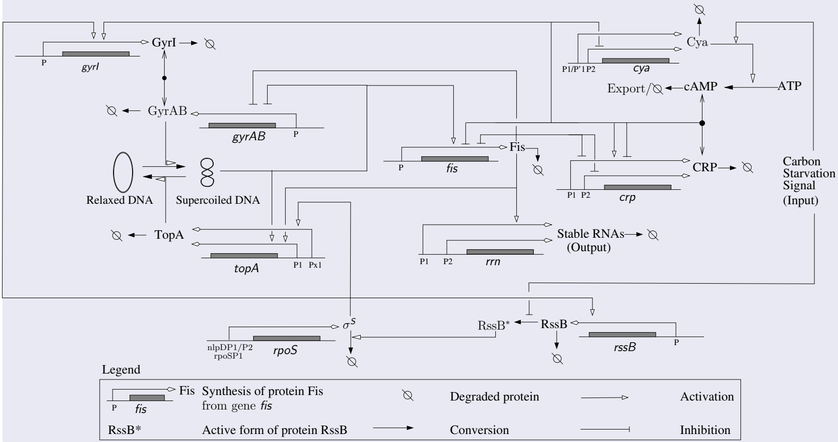


- Transition from exponential phase to stationary phase
- Changes in morphology, gene expression, ...
- Control of growth-phase transition by network of global regulators

# Carbon starvation response model in E.coli

## The network of global regulators



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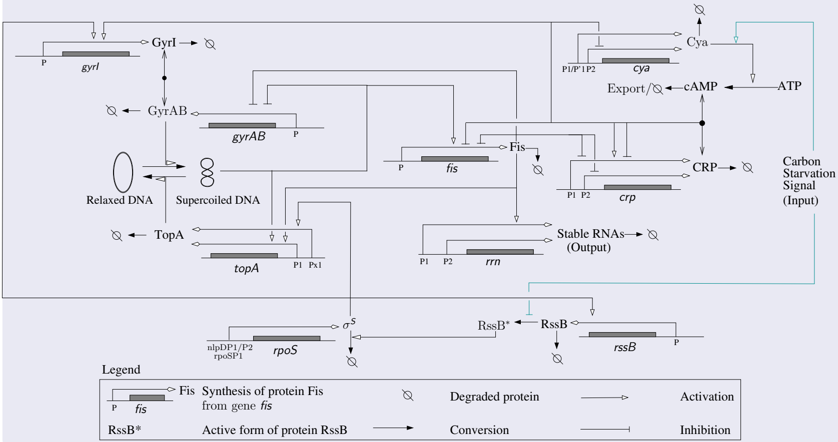

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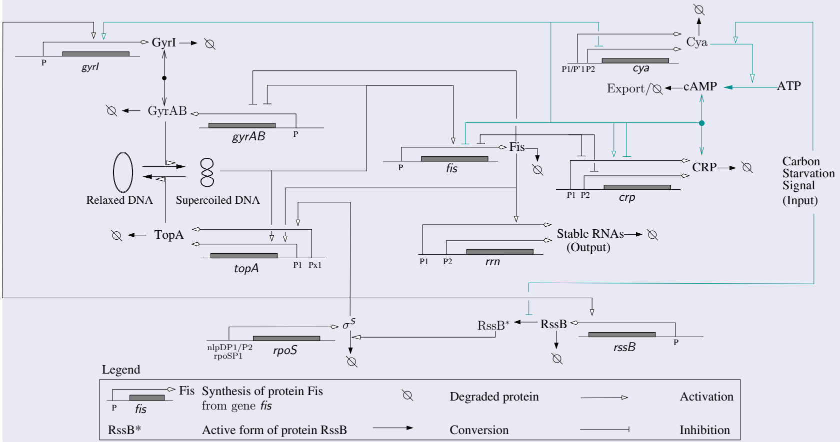

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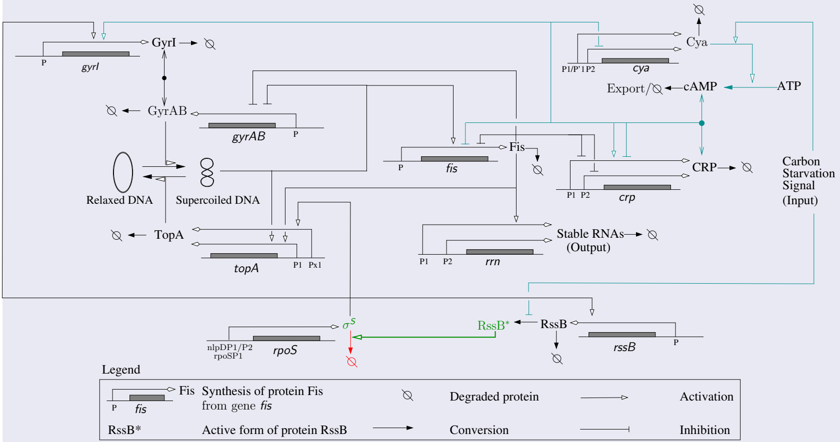

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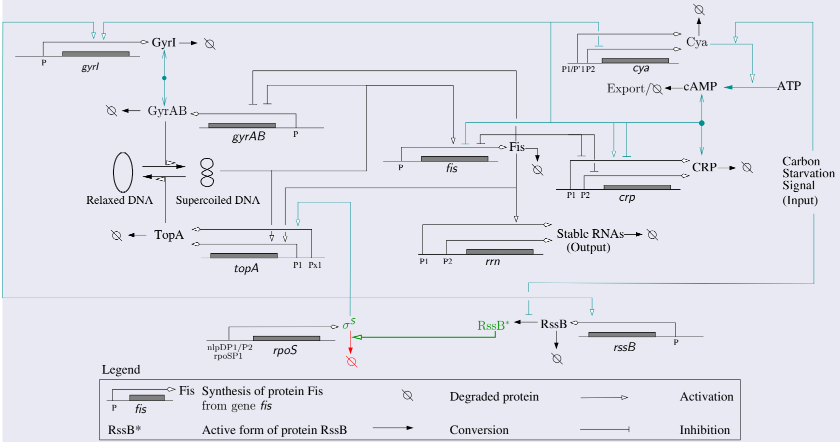

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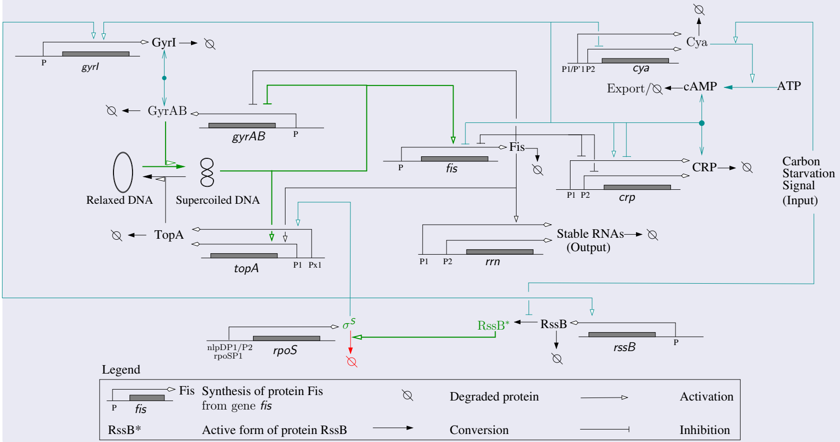

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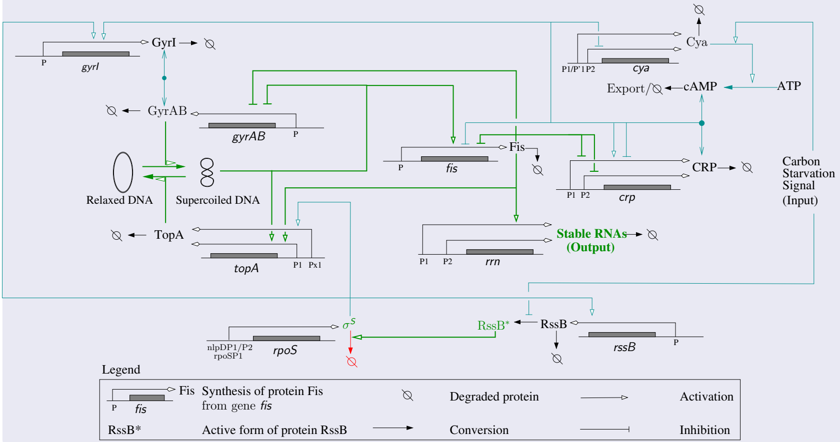

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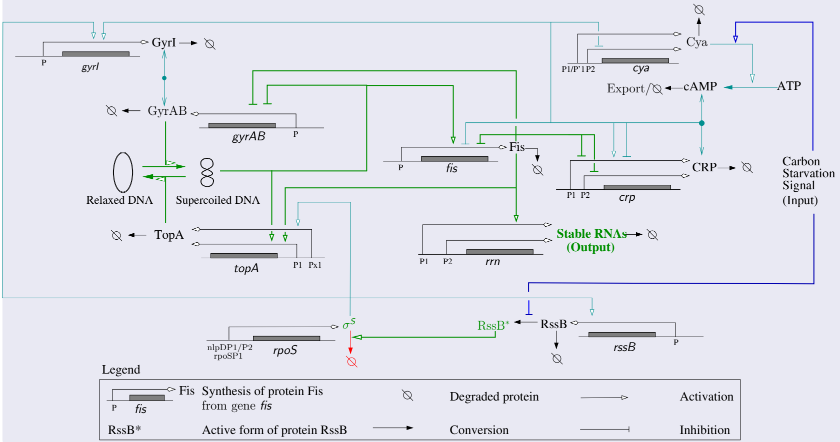

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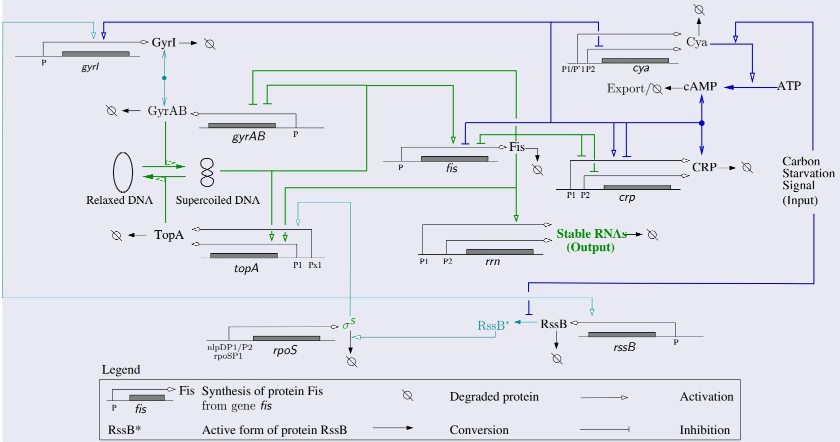

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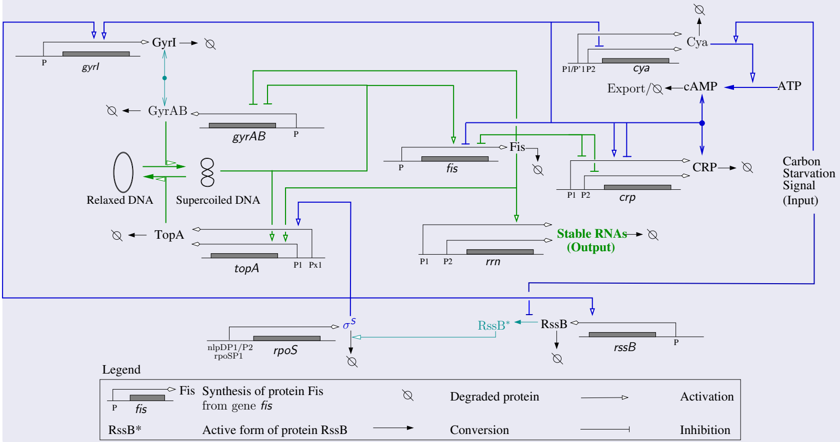

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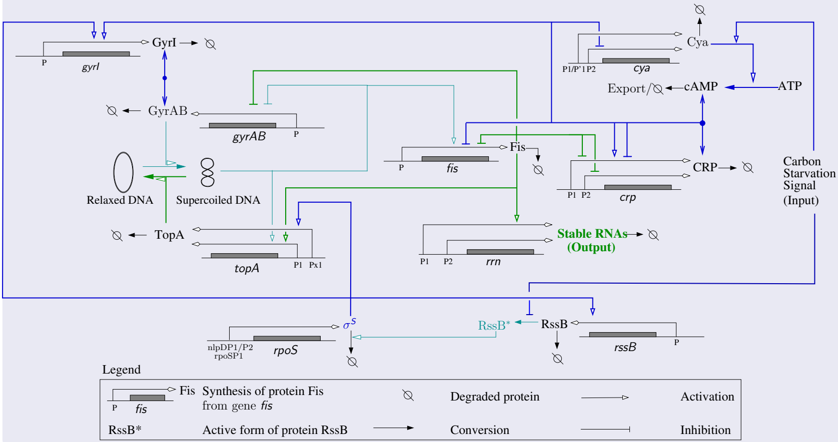

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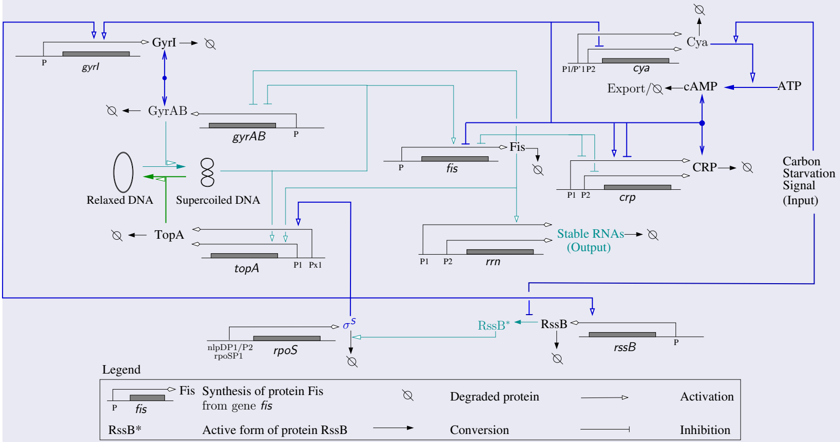

# Carbon starvation response model in E.coli

## Qualitative model

- Model of network of global regulators by means of piecewise-linear (PL) differential equations
- PL model provides coarse-grained picture of the dynamics of genetic regulatory networks

## Extension of model of carbon starvation response (Ropers et al. 2006)

- 9 coupled PL differential equations + 1 input variable

  $\dot{x}_{gyrAB} = \kappa_{gyrAB}\,(1-s^{+}(x_{gyrAB},\theta^{2}_{gyrAB})\,s^{-}(x_{gyrI},\theta^{1}_{gyrI})\,s^{-}(x_{topA},\theta^{1}_{topA}))\,s^{-}(x_{fis},\theta^{4}_{fis})-\gamma_{gyrAB}\,x_{gyrAB}$
- $\simeq$ 50 inequality constraints

  $0 < \theta^{1}_{gyrAB} < \theta^{2}_{gyrAB} < \kappa_{gyrAB}/\gamma_{gyrAB} < max_{gyrAB}$

## Qualitative simulation of carbon starvation response

- Qualitative simulation method and computer tool GNA used to analyze models
- Results in large state transition graphs ($\mathcal{O}(10^{3}) - \mathcal{O}(10^{10})$ states)

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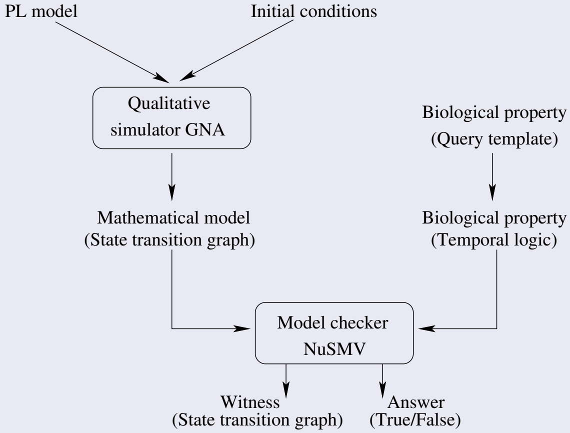
## Extended outline of approach

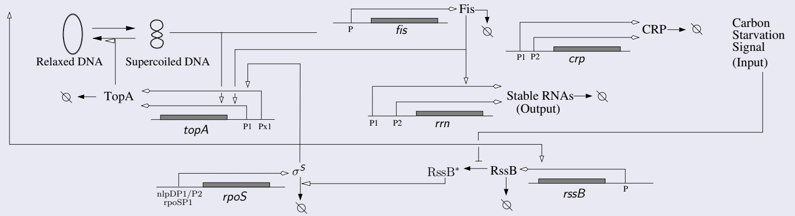


# Application to the carbon starvation response model in E.coli

## Biological question

Is the entry into stationary phase always preceded by the accumulation of the stress response regulator RpoS?

- In the presence of a carbon source, RpoS is degraded through the binding of the protein RssB
- The depletion of the carbon source inactivates RssB, thus allowing RpoS to accumulate
- Entry into stationary phase corresponds to downregulation of *rrn* operons



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## Sequence pattern

| A state | $x_{rrn} < \theta_{rrn}$ | is reached and is | necessarily | preceded | at some time | by a state | $x_{rpoS} \geq \theta^1_{rpoS}$ |

CTL: $EF\ (x_{rrn} < \theta_{rrn}) \wedge \neg E\ (\neg(x_{rpoS} \geq \theta^1_{rpoS})\ U\ (x_{rrn} < \theta_{rrn}))$

## Model-checker response

True

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## Occurrence/Exclusion pattern: "Mutual inhibition of Fis and CRP"

| It | is not possible | for a state | $x_{crp} \geq \frac{k^1_{crp}+k^2_{crp}+k^3_{crp}}{\gamma_{crp}} \wedge x_{fis} \geq \theta^4_{fis}$ | to occur | and |

| It | is not possible | for a state | $x_{crp} \leq \frac{k^1_{crp}}{\gamma_{crp}} \wedge x_{fis} \leq \theta^1_{fis}$ | to occur |

CTL: $\neg EF(x_{crp} \geq \frac{k^1_{crp}+k^2_{crp}+k^3_{crp}}{\gamma_{crp}} \wedge x_{fis} \geq \theta^4_{fis}) \wedge \neg EF(x_{crp} \leq \frac{k^1_{crp}}{\gamma_{crp}} \wedge x_{fis} \leq \theta^1_{fis})$

## Consequence pattern: "Damped oscillations after nutrient upshift"

| If a state | $x_{signal} < \theta_{signal}$ | occurs, then it is | necessarily | followed by a state | $isOscillatoryState$ |

CTL: $AG\ ((x_{signal} < \theta_{signal}) \Rightarrow AF\ (isOscillatoryState))$

## Invariance pattern: "Expression of topA during growth-phase transitions"

| A state | $x_{topA} < \theta^1_{topA}$ | can | persist indefinitely |

CTL: $EG\ (x_{topA} < \theta^1_{topA})$

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CTL: $\neg EF(x_{crp} \geq \frac{k^1_{crp}+k^2_{crp}+k^3_{crp}}{\gamma_{crp}} \wedge x_{fis} \geq \theta^4_{fis}) \wedge \neg EF(x_{crp} \leq \frac{k^1_{crp}}{\gamma_{crp}} \wedge x_{fis} \leq \theta^1_{fis})$

### Consequence pattern: "Damped oscillations after nutrient upshift"

| If a state | $x_{signal} < \theta_{signal}$ | occurs, then it is | necessarily | followed by a state | *isOscillatoryState* |

CTL: $AG\ ((x_{signal} < \theta_{signal}) \Rightarrow AF\ (isOscillatoryState))$

### Invariance pattern: "Expression of topA during growth-phase transitions"

| A state | $x_{topA} < \theta^1_{topA}$ | can | persist indefinitely |

CTL: $EG\ (x_{topA} < \theta^1_{topA})$

# Application to the carbon starvation response model in E.coli

### Occurrence/Exclusion pattern: "Mutual inhibition of Fis and CRP"

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## Outline


1. *Introduction*
   - Motivation: qualitative simulation of large genetic regulatory networks
   - Computational approach: formal verification

2. *Query patterns for formal verification*
   - Definition of patterns: why patterns?
   - Proposed patterns
   - Translation to temporal logic

3. *Analysis of the carbon starvation response in E.coli*
   - Carbon starvation response model
   - Analysis using query patterns

4. *Conclusions and perspectives*

# Conclusions

### *Increasingly large qualitative models*

Formal verification techniques are promising tools for upscaling the analysis of qualitative models of genetic regulatory networks

### *Difficulty to formulate appropriate questions in temporal logics*

Formulation of patterns in the form of query templates

- Capture most frequently-asked questions by modelers
- Automatic translation to several temporal logics

### *Compromise between patterns and temporal logic*

- Patterns help users formulate frequent queries
- But: they do not express all user queries

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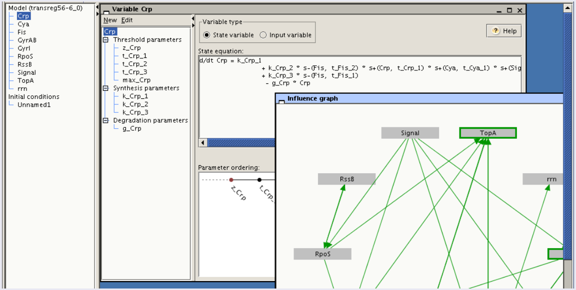
# Perspectives

## Environment for qualitative modeling and formal verification

Integration of the query patterns into the modeling tool GNA




## Query patterns in qualitative simulation

Generalization of query patterns to other qualitative reasoning applications

# *Perspectives*

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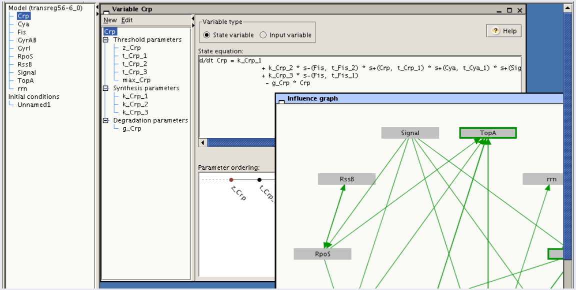


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## Thank you

Questions?