Model Checking Liveness Properties of Genetic Regulatory Networks

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Tools and Algorithms for Construction and Analysis of Systems
2007

Synthetic biology

- Synthetic biology: application of engineering approaches to produce novel artificial devices using biological building blocks

banana-smelling bacteria

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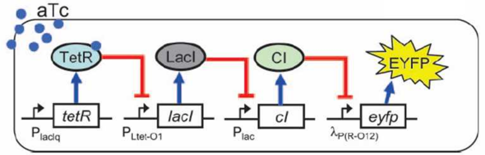
banana-smelling bacteria

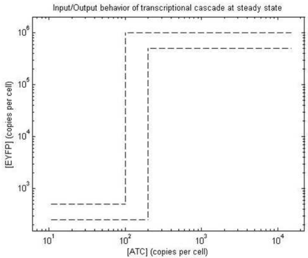
- Numerous potential engineering and medical applications
  - biofuel production, environment depollution, . . .
  - biochemical synthesis, tumor destruction, . . .

Need for rational design

- Gene networks are networks of genes, proteins, small molecules and their regulatory interactions



transcriptional cascade [Hooshangi *et al.*, PNAS 05]



ultrasensitive IO response

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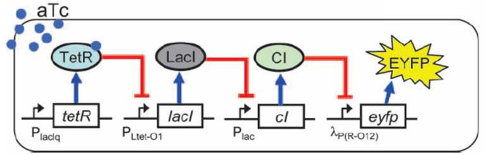

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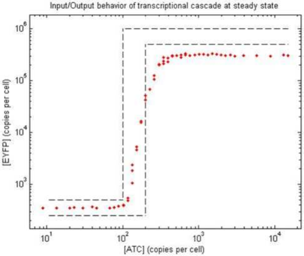

ultrasensitive IO response

- Network design is difficult

  Most newly-created networks are non-functioning and need tuning

Analysis of piecewise multi-affine (PMA) models

✠ Constraints: non-linear dynamical systems with uncertain parameters

- genetic regulations described by sigmoidal functions
- parameter uncertainties due to environmental fluctuations

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[Batt *et al.*, HSCC'07]

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[Batt *et al.*, HSCC'07]

✠ But: verification of liveness properties generally fails

- liveness properties state that something will eventually happen
- fails because quantitative aspects of time abstracted away: need to enforce progress of time in discrete abstraction

Outline

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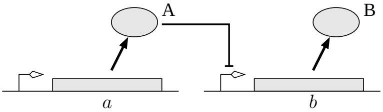
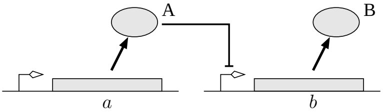
Gene network models



inhibition network

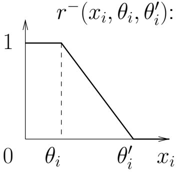
Gene network models



inhibition network

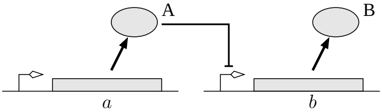
$$\dot{x}_a = \kappa_a - \gamma_a \, x_a$$
$$\dot{x}_b = \kappa_b \, r^-(x_a, \theta_a^1, \theta_a^2) - \gamma_b \, x_b$$

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



ramp functions for genetic regulations

Gene network models



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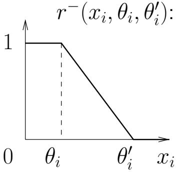
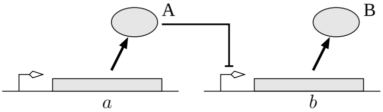


ramp functions for genetic regulations

- Check property: "At steady state, protein A concentration is high ($> \theta_a^2$) and protein B concentration is low ($< \theta_b$)"

Gene network models



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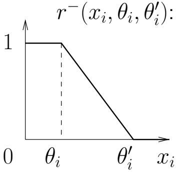
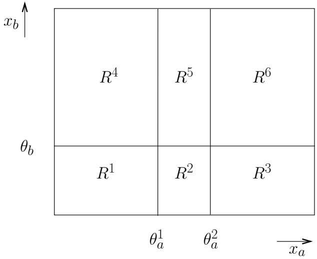


ramp functions for genetic regulations

- Check property: "At steady state, protein A concentration is high ($> \theta_a^2$) and protein B concentration is low ($< \theta_b$)" for every parameter $p = (\kappa_a, \kappa_b) \in P = [14, 18] \times [10, 15]$

PMA systems

- Partition of the state space: rectangles $R \in \mathcal{R}$



$$
\begin{aligned}
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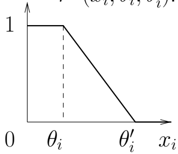
$r^-(x_i, \theta_i, \theta_i')$:



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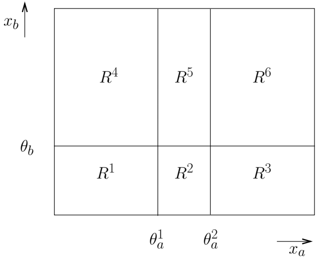

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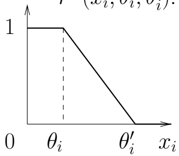

- Differential equation models $\dot{x} = f(x, p)$, where

  f is piecewise multiaffine function of state vector $x \in \mathcal{X}$

  f is affine function of parameter vector $p \in \mathcal{P}$ (κ's and γ's)

  (multiaffine: products of different variables allowed)

LTL specifications of dynamical properties

✠ Dynamical properties expressed in temporal logic LTL

- set of atomic proposition Π: $x_i < \lambda_i, \; x_i > \lambda_i$
- usual logical operators: $\neg\phi, \; \phi_1 \wedge \phi_2, \; \phi_1 \vee \phi_2, \; \phi_1 \rightarrow \phi_2$
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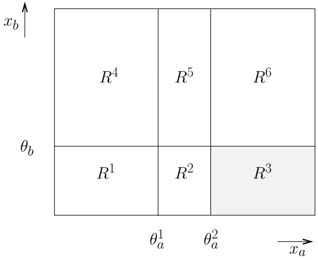

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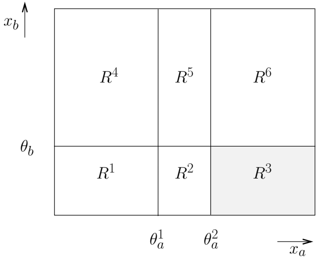

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✠ PMA system $\Sigma = (f, \Pi)$ satisfy property ϕ for parameter $p \in P$ iff $T_{\mathcal{X}}(p) \models \phi$ with $T_{\mathcal{X}}(p)$ embedding transition system

Discrete abstraction

- PMA system Σ and parameter set P associated with discrete abstraction $T^{\exists}_{\mathcal{R}}(P) = (\mathcal{R}, \rightarrow^{\exists}_{\mathcal{R},P}, \models_{\mathcal{R}})$, where
  - $\mathcal{R}$ finite set of rectangles

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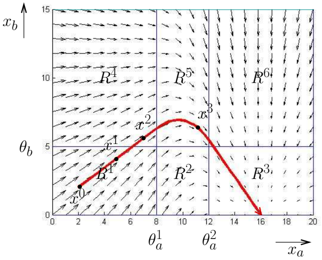
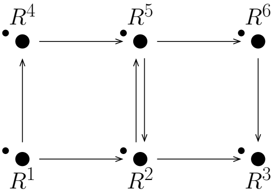


$p = (16, 12)$, $x^0 = (2, 2)$

transition between same or adjacent rectangles R and R' iff for some $p \in P$ there exists a solution going from R to R'



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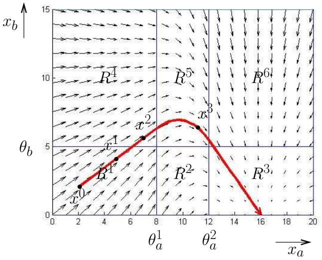

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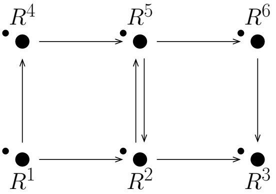

$R^1 \not\models_{\mathcal{R}}$ '$x_a > \theta_a^2$'
$R^1 \models_{\mathcal{R}}$ '$x_b < \theta_b$'

Model checking using discrete abstraction

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- $T^{\exists}_{\mathcal{R}}(P)$ can be used for proving universal properties of original system Σ for sets of parameters

  if $T^{\exists}_{\mathcal{R}}(P) \models \phi$, then $\forall p \in P$, $T_{\mathcal{X}}(p) \models \phi$

[Batt *et al.*, HSCC'07]

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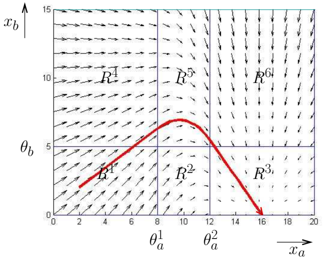
- But: verification may fail because of spurious executions

  if $T^{\exists}_{\mathcal{R}}(P) \not\models \phi$, then no conclusion !

Outline

Liveness checking

- Model checking liveness properties generally fails



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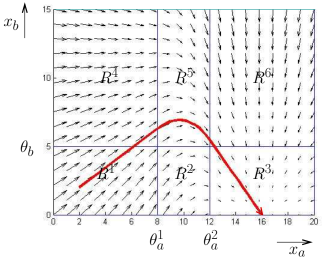

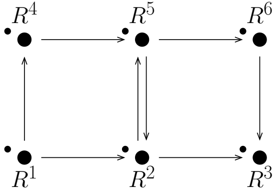

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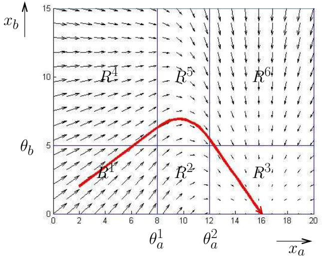

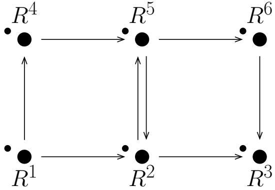

"Eventually, the system will remain in R^3" $\mathrm{F}\,\mathrm{G}\,(x_a > \theta_a^2 \wedge x_b < \theta_b)$

False! counter-examples:

$$e_{\mathcal{R}1} = (R^1, R^1, R^1, \ldots)$$
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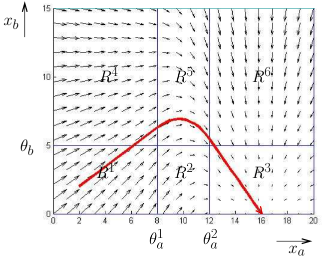

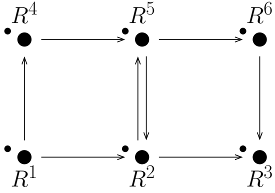

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✠ These counter-examples are spurious!

Transient regions

Definition

Let $p \in \mathcal{P}$ *and* $U \subseteq \mathcal{X}$. U *is transient for parameter* p *if for every solution* ξ *such that* $\xi(0) \in U$, *there exists* $\tau > 0$ *such that* $\xi(\tau) \notin \overline{U}$.

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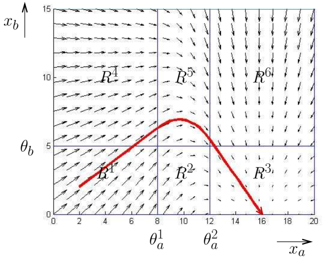

all the regions not containing R^3 are transient

Time-diverging executions

Definition

Let $P \subseteq \mathcal{P}$. *An execution* $e_{\mathcal{R}} = (R_0, R_1, \ldots)$ *of* $T^{\exists}_{\mathcal{R}}(P)$ *is time-diverging iff for some* $p \in P$, *there exist a solution* ξ *and a sequence of time instants* $\tau = (\tau_0, \tau_1, \ldots)$ *such that* $\lim_{i \to \infty} \tau_i = \infty$ *and* $\xi(\tau_i) \in R_i$, *for all* $i \geq 0$.

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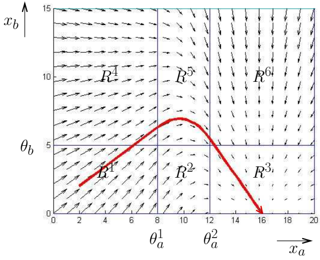

$e_{\mathcal{R}1} = (R^1, R^1, R^1, \ldots)$ and
$e_{\mathcal{R}2} = (R^2, R^5, R^2, R^5, \ldots)$
are time-converging executions

Transient regions and time-converging executions

- An execution $e_{\mathcal{R}}$ remains eventually always in a strongly connected component (SCC) of $T^{\exists}_{\mathcal{R}}(P)$, $SCC(e_{\mathcal{R}}) \subseteq \mathcal{X}$

Transient regions and time-converging executions

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- $SCC(e_{\mathcal{R}})$ cannot be transient if $e_{\mathcal{R}}$ is time-diverging!

Proposition

Let $P \subseteq \mathcal{P}$ and $e_{\mathcal{R}}$ be an execution of $T^{\exists}_{\mathcal{R}}(P)$. If $SCC(e_{\mathcal{R}})$ is transient for all $p \in P$, then $e_{\mathcal{R}}$ is time-converging.

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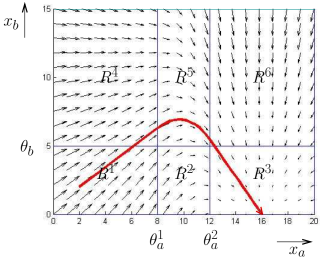
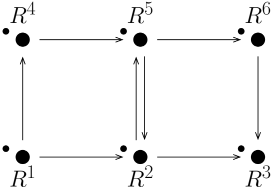


$SCC(e_{\mathcal{R}1}) = \{R^1\}$ and
$SCC(e_{\mathcal{R}2}) = \{R^2, R^5\}$ are transient regions
So $e_{\mathcal{R}1}$ and $e_{\mathcal{R}2}$ are time-converging

Ruling-out time-converging executions

- Approach (assuming that transient regions can be computed)
  1. compute discrete abstraction $T_{\mathcal{R}}^{\exists}(P)$ and its SCCs



SCCs: $\{R^1\}\,\{R^2, R^5\}\,\{R^3\}\,\{R^4\}\,\{R^6\}$

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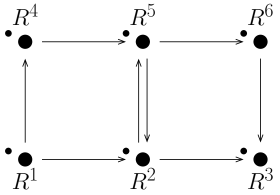
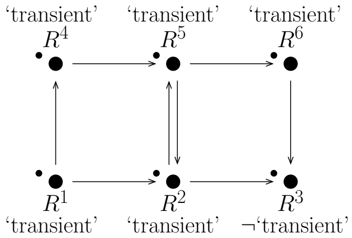
  2. test whether SCCs are transient or not



SCCs:	$\{R^1\}$	$\{R^2, R^5\}$	$\{R^3\}$	$\{R^4\}$	$\{R^6\}$
transient?	Y	Y	N	Y	Y

Ruling-out time-converging executions

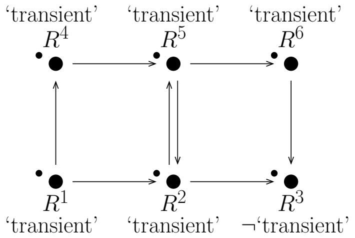
- Approach (assuming that transient regions can be computed)
  1. compute discrete abstraction $T_{\mathcal{R}}^{\exists}(P)$ and its SCCs
  2. test whether SCCs are transient or not
  3. label every rectangle in a transient SCC by 'transient', and test whether $T_{\mathcal{R}}^{\exists}(P) \models \phi'$, where $\phi' = (\neg \mathrm{F}\,\mathrm{G}\,\text{'transient'}) \rightarrow \phi$



$T_{\mathcal{R}}^{\exists}(P) \models \phi'$? with $\phi' =$
$(\neg \mathrm{F}\,\mathrm{G}\,\text{'transient'}) \rightarrow \mathrm{F}\,\mathrm{G}\,(x_a > \theta_a^2 \wedge x_b < \theta_b)$

Ruling-out time-converging executions

- Approach (assuming that transient regions can be computed)
  1. compute discrete abstraction $T^{\exists}_{\mathcal{R}}(P)$ and its SCCs
  2. test whether SCCs are transient or not
  3. label every rectangle in a transient SCC by 'transient', and test whether $T^{\exists}_{\mathcal{R}}(P) \models \phi'$, where $\phi' = (\neg \mathrm{F}\,\mathrm{G}\,\text{'transient'}) \rightarrow \phi$



$T^{\exists}_{\mathcal{R}}(P) \models \phi'$? with $\phi' =$
$(\neg \mathrm{F}\,\mathrm{G}\,\text{'transient'}) \rightarrow \mathrm{F}\,\mathrm{G}\,(x_a > \theta_a^2 \wedge x_b < \theta_b)$

True!

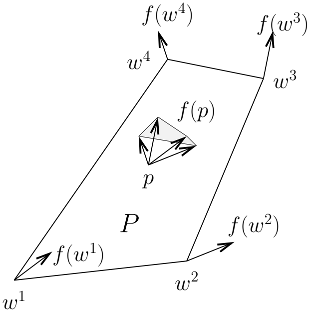
Outline

Transient region computation for PMA systems

Convexity properties of affine and multiaffine functions

- *Let f be an affine function and P be a polytope. Then, $\forall p \in P$, $f(p) \in \mathrm{hull}(\{f(w) \mid w \in \mathcal{V}_P\})$.*

[Habets et al., Trans Aut Contr, 06]



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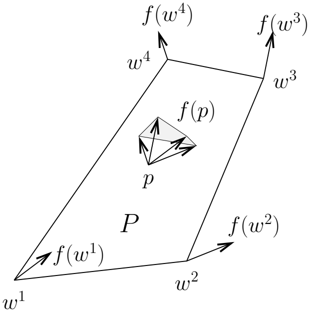
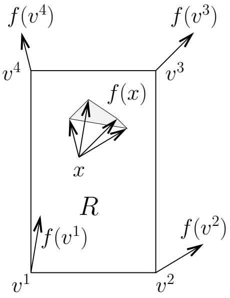
- *Let f be a multiaffine function and R be a hyperrectangle. Then, $\forall x \in R$, $f(x) \in \mathrm{hull}(\{f(v) \mid v \in \mathcal{V}_R\})$.*

  [Belta and Habets, Trans Aut Contr, 06]

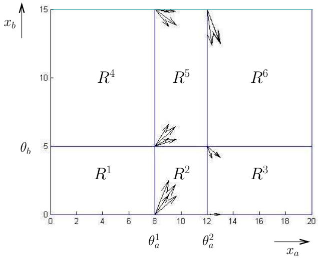




Transient region computation for PMA systems

Proposition

Let $P \subseteq \mathcal{P}$ be a polytope and U a union of rectangles.
If $0 \notin \mathrm{hull}(\{f(v,w) \mid v \in \mathcal{V}_R, R \subseteq U, w \in \mathcal{V}_P\})$, then U is transient for all parameters $p \in P$.



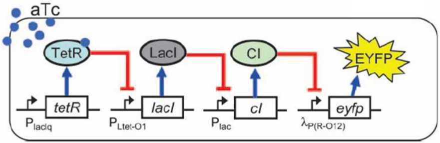
$x \in R^2 \cup R^5$,
$p \in P = [14, 18] \times [8, 14]$
$R^2 \cup R^5$ is transient for all $p \in P$

- Decidable by solving linear optimization problem
- Implemented in RoVerGeNe (Robust Verification of Gene Networks)

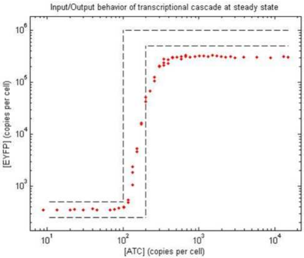
Outline

Robustness analysis of transcriptional cascade

- Previous analysis of synthetic transcriptional cascade suggested parameter modifications for network tuning



transcriptional cascade



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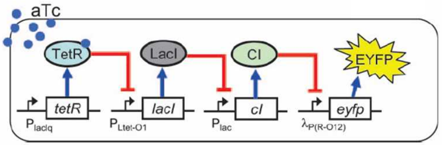

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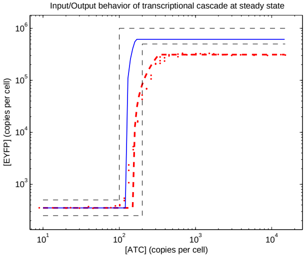

ultrasensitive IO response

$$\begin{aligned}
\dot{x}_{tetR} &= \kappa_{tetR} - \gamma_{tetR}\, x_{tetR},\\
\dot{x}_{lacI} &= \kappa^0_{lacI} + \kappa_{lacI}(1 - r^+(x_{tetR}, \theta^1_{tetR}, \theta^2_{tetR})\, r^-(u_{aTc}, \theta^1_{aTc}, \theta^2_{aTc})) - \gamma_{lacI}\, x_{lacI}\\
\dot{x}_{cI} &= \kappa^0_{cI} + \kappa_{cI}\, r^-(x_{lacI}, \theta^1_{lacI}, \theta^2_{lacI}) - \gamma_{cI}\, x_{cI}\\
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\end{aligned}$$

PMA model

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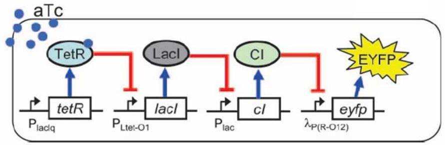

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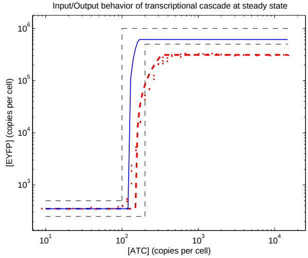

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PMA model

- Does modified network behave robustly?

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- Approach can prove non-trivial liveness property of a 5-dimensional state space and 11-dimensional parameter space system in < 4 hrs

Outline

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- Approach implemented in RoVerGeNe and applied to analysis of synthetic gene network

  Approach can answer efficiently non-trivial questions on networks of biological interest

Discussion

✠ Related work:

- spurious behaviors introduced by abstraction process ruled out using fairness constraints
  [Bouajjani *et al.*, SAS'01], [Dams *et al.*, WAVe'00]
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- Future research directions:
  - application to other classes of hybrid systems
  - use abstraction that preserves quantitative aspects of time: timed abstraction

Acknowledgements

Thank you for your attention!

see also Model checking genetic regulatory networks with parameter uncertainty, HSCC'07
G. Batt, C. Belta and R. Weiss