On Solving Temporal Logic Constraints in Constrained Transition Systems

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CP meets CAV
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Outline

Motivation: Analysis/Synthesis of Gene/Protein Networks

States and Transitions as Constraints over $\mathbb{R}_{\text{lin}}$

Temporal Logic Constraints over $\mathbb{R}_{\text{lin}}$

Implementation of FOCTL($\mathbb{R}_{\text{lin}}$)

Conclusion

Outline

Systems Biology

System-level understanding of high-level cell functions from their biochemical basis at the molecular level [Kitano 2000]

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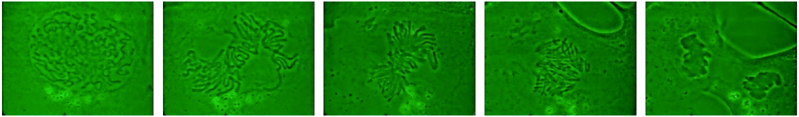

gene transcription, protein degradation and enzymatic reactions

$$\mathsf{S} + \mathsf{E} \underset{k_1}{\overset{k_2}{\leftrightarrows}} \mathsf{ES} \xrightarrow{k_3} \mathsf{E} + \mathsf{P}$$

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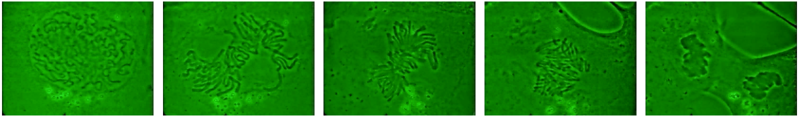

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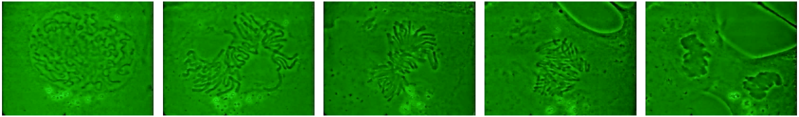

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Ordinary Differential Equations

$$\begin{aligned}
\dot{S} &= -k_1 * S * E + k_2 * ES \\
\dot{P} &= k_3 * ES \\
\dot{E} &= -k_1 * S * E + (k_2 + k_3) * ES \\
\dot{ES} &= k_1 * S * E - (k_2 + k_3) * ES
\end{aligned}$$

Continuous-Time Markov Chain

A Logical Paradigm for Systems and Synthetic Biology

Biological Model = *(Quantitative) State Transition System* K

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- Expression of high-level specifications
- Model-checking can be efficient on large complex systems
- Temporal logic with numerical constraints can deal with continuous time models (ODE or CTMC, hybrid systems)

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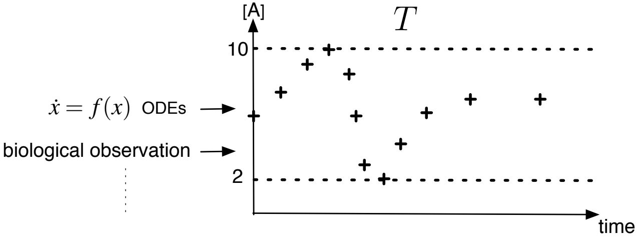
Query language for large reaction networks [Eker et al. PSB 02, Chabrier Fages CMSB 03, Batt et al. Bi 05]
Analysis of experimental data time series [Fages Rizk CMSB 07]
Kinetic parameter search [Bernot et al. JTB 04] [Calzone et al. TCSB 06] [Rizk et al. 08 CMSB]
Robustness analysis [Batt et al. 07] [Rizk et al. 09 ISMB]

Temporal Logic with constraints over $\mathbb{R}$



- **F**([A]>10) : the concentration of A eventually gets above 10.
- **FG**([A]>10) : the concentration of A eventually reaches and remains above value 10.
- **F**(Time=t1∧[A]=v1 ∧ **F**(.... ∧ **F**(Time=tN∧[A]=vN)...))
  Numerical data time series (e.g. experimental curves)
- Local maxima, oscillations, period constraints, etc.

True/False valuation of temporal logic formulae

The **True/False** valuation of temporal logic formulae is **not well suited** to several problems :

- parameter search, optimization and control of continuous models
- quantitative estimation of robustness
- sensitivity analyses

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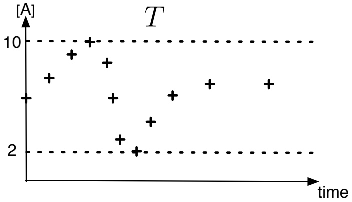
$\rightarrow$ need for a continuous degree of satisfaction of temporal logic formulae

How far is the system from verifying the specification ?

From Model-Checking to TL Constraint Solving



$LTL(\mathbb{R})$

$\Phi = F([A] \geq 7 \wedge F([A] \leq 0))$

Model-checking

the formula is false

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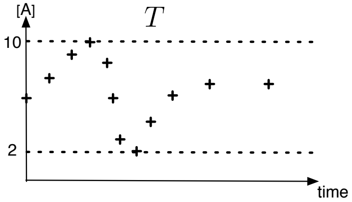

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Φ=F([A]≥7
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Φ*=F([A]≥x
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Constraint solving

the formula is true for any
x≤10 ∧ y≥2

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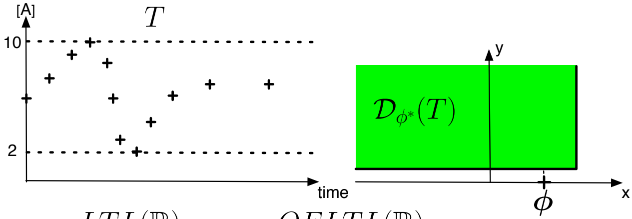

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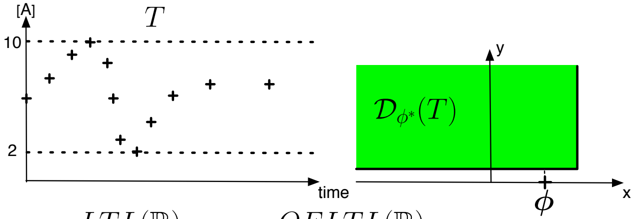


$LTL(\mathbb{R})$	$QFLTL(\mathbb{R})$
Φ=F([A]≥7 ∧F([A]≤0))	Φ*=F([A]≥x ∧F([A]≤y))
Model-checking	**Constraint solving**
the formula is false vd=2 **sd=1/3**	the formula is true for any x≤10 ∧ y≥2

Validity domain for the free variables [Fages Rizk CMSB'07, TCS 11]

Violation degree $vd(T,\phi) = \text{distance}(val(\phi), D_{\phi^*}(T))$

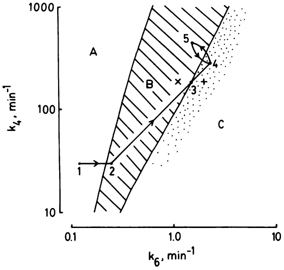
Satisfaction degree $sd(T,\phi) = \frac{1}{1+vd(T,\phi)} \in [0,1]$

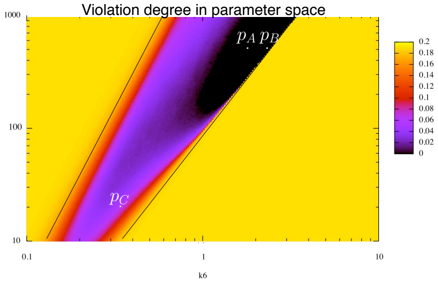
Bifurcation Diagrams and LTL($\mathbb{R}$) Satisfaction Diagrams

Example with :

- yeast cell cycle model [Tyson PNAS 91]
- oscillation of at least 0.3

$$\phi^*: \mathbf{F}(\ [A]>x \wedge \mathbf{F}([A]<y)\ );\ \text{amplitude } x\text{-}y \geq 0.3$$

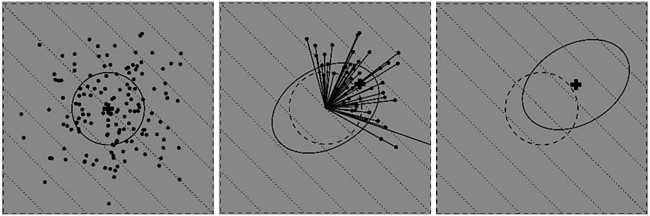




Bifurcation diagram LTL($\mathbb{R}$) satisfaction diagram

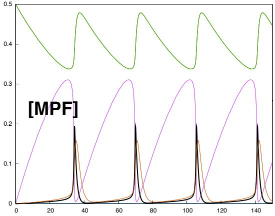
Parameter Inference by Local Search

- LTL($\mathbb{R}$) satisfaction degree as black-box fitness function (computed by TL constraint solving)
- Other constraints on parameter range, inequalities,... added to the fitness function
- Covariance Matrix Adaptation Evolution Strategy (CMA-ES) [Hansen Osermeier 01, Hansen 08]: probabilistic neighborhood updated in covariance matrix at each move



Kinetic Parameter Inference from LTL($\mathbb{R}$) Spec.

- yeast cell cycle control model [Tyson PNAS 91]
- 6 variables, 8 kinetic parameters



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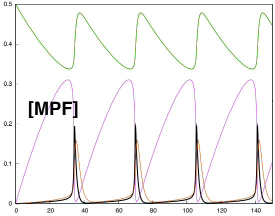

- Pb : find values of 8 parameters such that amplitude is ≥ 0.3
  ϕ^*: **F**([A]>x $\wedge$ **F**([A]<y))
  amplitude z=x-y
  goal : z = 0.3

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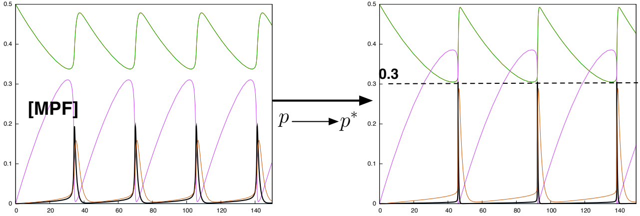

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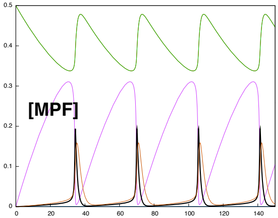
  ϕ^*: **F**([A]>x $\wedge$ **F**([A]<y))
  amplitude z=x-y
  goal : z $=$ 0.3
- $\rightarrow$ solution found after 30s (100 calls to the fitness function)

Kinetic Parameter Search from Period Constraints



- Pb : find values of 8 parameters such that period is 20

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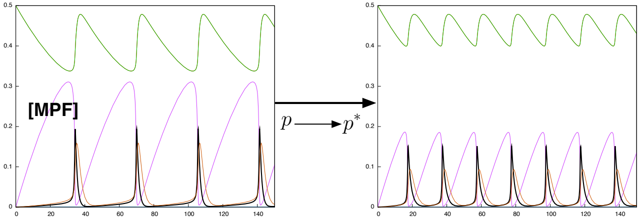
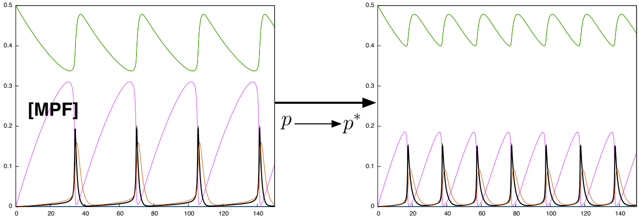


- Pb : find values of 8 parameters such that period is 20
- $\rightarrow$ Solution found after 60s (200 calls to the fitness function)

Kinetic Parameter Search from Period Constraints



- Pb : find values of 8 parameters such that period is 20
- $\rightarrow$ Solution found after 60s (200 calls to the fitness function)
- Scales up to 50-100 parameters.
- Linear speed-up on a cluster of 10000 cores. Parallelization of parameter sets and multiconditions for mutants.

Robustness Measure

Robustness defined as mean functionality with respect to :

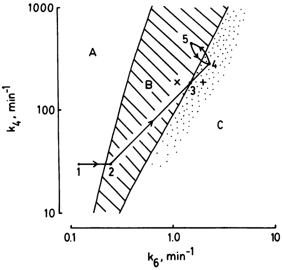
- a biological system
- a functionality property ϕ
- a set P of perturbations

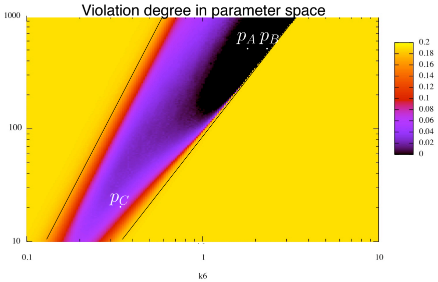
Measure of robustness w.r.t. LTL($\mathbb{R}$) spec:

$$\mathcal{R}_{\phi,P} = \int_{p \in P} sd(\phi, T(p)) \; prob(p) \; dp$$

where $T(p)$ is the trace obtained by numerical integration of the ODE for perturbation p of the parameters
$\longrightarrow$ estimated by sampling

Example on Cell Cycle Control

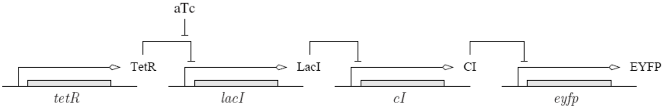


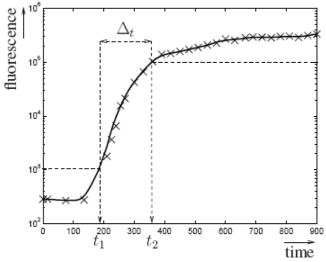


$$\mathcal{R}_{\phi,p_A} = 0.83,\ \mathcal{R}_{\phi,p_B} = 0.43,\ \mathcal{R}_{\phi,p_C} = 0.49$$

Example on a Synthetic Toggle Switch for *E. Coli*

Cascade of transcriptional inhibitions added to *E.coli* [Weiss et al PNAS 05] **input** small molecule aTc **output** protein EYFP





Specification: EYFP has to remain below 10^3 for at least 150 min., then exceeds 10^5 after at most 450 min., and switches from low to high levels in less than 150 min.

Specification in FOLTL($\mathbb{R}$)

The timing specifications can be formalized in temporal logic as follows:

$$\begin{aligned}\phi(t_1, t_2) = & \quad \mathbf{G}(\mathit{time} < t_1 \rightarrow [\mathrm{EYFP}] < 10^3) \\ \wedge & \quad \mathbf{G}(\mathit{time} > t_2 \rightarrow [\mathrm{EYFP}] > 10^5) \\ \wedge & \quad t_1 > 150 \wedge t_2 < 450 \wedge t_2 - t_1 < 150\end{aligned}$$

which is abstracted into

$$\begin{aligned}\phi(t_1, t_2, b_1, b_2, b_3) = & \quad \mathbf{G}(\mathit{time} < t_1 \rightarrow [\mathrm{EYFP}] < 10^3) \\ \wedge & \quad \mathbf{G}(\mathit{time} > t_2 \rightarrow [\mathrm{EYFP}] > 10^5) \\ \wedge & \quad t_1 > b1 \wedge t_2 < b_2 \wedge t_2 - t_1 < b_3\end{aligned}$$

for computing validity domains for b_1, b_2, b_3

with the objective $b_1 = 150, b_2 = 450, b_3 = 150$
for computing the satisfaction degree in a given trace.

Improving robustness

Variance-based global sensitivity indices $S_i = \frac{Var(E(R|P_i))}{Var(R)} \in [0,1]$

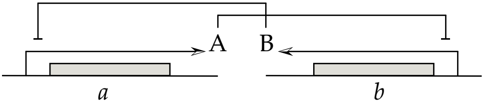
S_γ	20.2 %	$S_{\kappa_{eyfp},\gamma}$	8.7 %
$S_{\kappa_{eyfp}}$	7.4 %	$S_{\kappa_{cl},\gamma}$	6.2 %
$S_{\kappa_{cl}}$	6.1 %	$S_{\kappa^0_{cl},\gamma}$	5.0 %
$S_{\kappa^0_{lacl}}$	3.3 %	$S_{\kappa^0_{cl},\kappa_{eyfp}}$	2.8 %
$S_{\kappa^0_{cl}}$	2.0 %	$S_{\kappa_{cl},\kappa_{eyfp}}$	1.8 %
$S_{\kappa_{lacl}}$	1.5 %	$S_{\kappa^0_{eyfp},\gamma}$	1.5 %
$S_{\kappa^0_{eyfp}}$	0.9 %	$S_{\kappa^0_{cl},\kappa_{cl}}$	1.1 %
$S_{u_{aTc}}$	0.4 %	$S_{\kappa^0_{cl},\kappa_{lacl}}$	0.5 %
total first order	40.7 %	total second order	31.2 %

degradation factor γ has the strongest impact on the cascade.

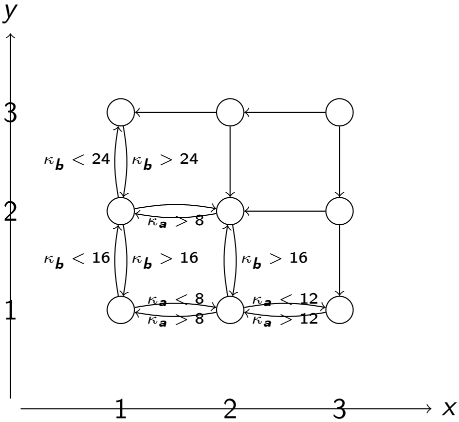
aTc variations have a very low impact

different importance of the basal κ^0_{eyfp} and regulated κ_{eyfp} EYFP production rates

Constraints on Transitions in Piecewise Multi-affine Models



$$\dot{x}_a = \kappa_a r_a(x_b, \theta_b, \theta'_b) - \gamma_a x_a$$
$$\dot{x}_b = \kappa_b r_b(x_a, \theta_a, \theta'_a) - \gamma_b x_b$$



FOCTL queries:

Reachability

? $EF(X = 3)$

Enumeration of stable states:

? $X = V \wedge AX(X = V)$

$X = V = 1 \wedge \kappa_a < 8 \wedge \kappa_b < 16$

$X = V = 2 \wedge 8 < \kappa_a < 12 \wedge \kappa_b < 16$

$X = V = 3 \wedge 12 < \kappa_a$

$X = V = 4 \wedge \kappa_a < 8 \wedge 16 < \kappa_b < 24$

$X = V = 7 \wedge 24 < \kappa_b$

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- Set of ground states: $|s|_{\mathcal{D}} = \{\rho(\vec{x}) \mid \rho : X \longrightarrow \mathcal{D},\ \mathcal{D} \models \rho(s)\}$

Transitions as Constraints

- Finite set of primed state variables: $\vec{x}'$
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- A CTS r is finitary (resp. bounded) if for any s the set of predecessors $\{\exists \vec{x}'(r^i \wedge s[\vec{x}'/\vec{x}])\}_{i \geq 1}$ is finite (bounded card.).

$\mathbb{R}_{\mathsf{lin}}$ Linear Arithmetic over the Reals

- Atomic constraints in $\mathbb{R}_{\mathsf{lin}}$ are inequalities over linear combination of variables

$$2 * x + 4 * y \leq 5$$

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- The conjunction of constraints $a \wedge b$ admits for solutions the intersection of the polyhedra solutions of a and b which is a polyhedron.

FO($\mathbb{R}_{\text{lin}}$) through Finite Unions of Polyhedra

Disjunction $\vee$ A disjunction of conjunctions of linear arithmetic constraints is a finite union of polyhedra and $(\bigcup_i A_i) \cap \left(\bigcup_j B_j\right) = \bigcup_{i,j}(A_i \cap B_j)$

Negation $\neg$ The complement of a polyhedron is a union of polyhedra
The complement of a union of polyhedra is the intersection of the complements of each polyhedron

Existential $\exists$ Projection to the subspace of the other dimensions

Universal $\forall$ $\neg\exists x(\neg c)$

Equality $=$ double inclusion $U \cap \overline{V} = \overline{U} \cap V = \emptyset$

Outline

First-Order Computation Tree Logic FOCTL($\mathcal{D}$)

$$
\begin{aligned}
CTL ::= \;& \mid c \\
& \mid \phi \wedge \psi \mid \phi \vee \psi \mid \neg\phi \mid \exists x \phi \mid \forall x \phi \\
& \mid \mathsf{E}X(\phi) \mid \mathsf{E}F(\phi) \mid \mathsf{E}G(\phi) \\
& \mid \mathsf{A}X(\phi) \mid \mathsf{A}F(\phi) \mid \mathsf{A}G(\phi)
\end{aligned}
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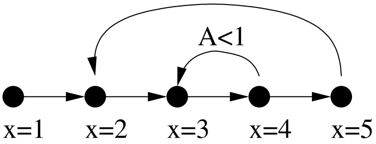
Example:



$\mathrm{E}G(x \leq V)$?

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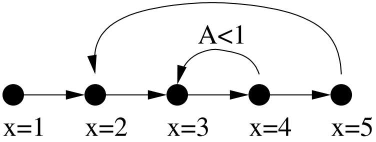
\begin{aligned}
CTL ::= \; & \mid c \\
& \mid \phi \wedge \psi \mid \phi \vee \psi \mid \neg\phi \mid \exists x \phi \mid \forall x \phi \\
& \mid \mathsf{E}X(\phi) \mid \mathsf{E}F(\phi) \mid \mathsf{E}G(\phi) \\
& \mid \mathsf{A}X(\phi) \mid \mathsf{A}F(\phi) \mid \mathsf{A}G(\phi)
\end{aligned}
$$

Example:



$$\mathsf{E}G(x \leq V) \;?$$
$$(V \geq 5) \vee (1 \leq x \leq 4 \wedge V \geq 4 \wedge A < 1)$$

FOCTL Constraint Solving Fixpoint Algorithm

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Complexity

For a bounded CTS r with maximum cardinality K for the set of predecessor state constraints for any state constraint

the time complexity for deciding the $\mathcal{D}$-satisfiability of ϕ in r with an oracle constraint solver for $\mathcal{D}$ is

$$O(|\phi| * K^2)$$

(what is implemented in FOCTL($\mathbb{R}_{\text{lin}}$))

$$O(|\phi| * K)$$

for traces of length K without branching
(what is implemented in Biocham)

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- idem for $ag(s)$

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- partitionning of discrete dimensions where the variable x always appears in the form $x = \mathit{constant}$.

Computation Results

Comparison to Delzanno and Podelski's CLP($\mathbb{R}$) implementation on an Intel(R) Core(TM)2 CPU at 1.86GHz with 2GB of RAM.

	CLP($\mathbb{R}$)	FOCTL($\mathbb{R}_{\text{lin}}$)
bakery	0.69	2.29
bakery3	12.47	3.15
bakery4	47.73	4.21
ticket	0.64	2.76 (widening)
bbuffer1	4.09	3.70
bbuffer2	0.67	6.80
ubuffer	4.49	2.93 (widening)
insertion	0.02	4.43 (widening)
selection	0.02	10.21
mesi	1.03	5.56
matrix-mul 0	.02	16.07
csm	3.81	7.88

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- Hybrid computation domains ? (FO)CTL($\mathbb{R}_{lin}$,f,Graph,FD) ?