Digital/Analog Computation in the Cell

Computational Systems Biology and Optimization

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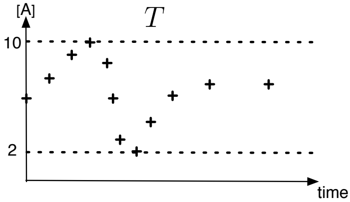
Specification of Dynamical Behaviors in LTL($\mathbb{R}$)



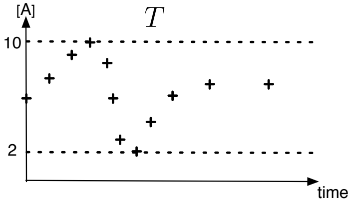
$LTL(\mathbb{R})$

Φ=F([A]≥7
∧F([A]≤0))

Model-checking

the formula is false

Model-Checking generalized to Contraint Solving



$LTL(\mathbb{R})$

Φ=F([A]≥7 ∧F([A]≤0))

Model-checking

the formula is false

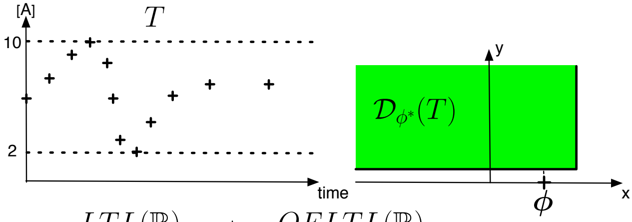
$QFLTL(\mathbb{R})$

Φ*=F([A]≥x ∧F([A]≤y))

Constraint solving

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

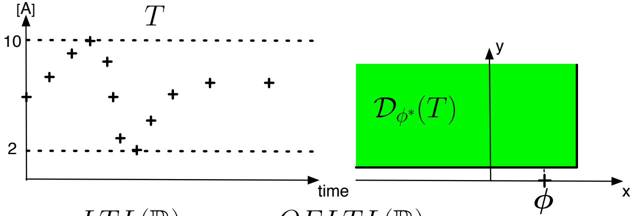
Model-Checking generalized to Contraint Solving



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

Validity domain $\mathcal{D}_{\phi^*}(T)$ of **free variables** in ϕ^* [Fages Rizk TCS'08]

Continuous Satisfaction Degree



$LTL(\mathbb{R})$

Φ=F([A]≥7 ∧F([A]≤0))

Model-checking

the formula is false vd=2 **sd=1/3**

$QFLTL(\mathbb{R})$

Φ*=F([A]≥x ∧F([A]≤y))

Constraint solving

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

Validity domain $\mathcal{D}_{\phi^*}(T)$ of **free variables** in ϕ^* [Fages Rizk TCS'08]

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

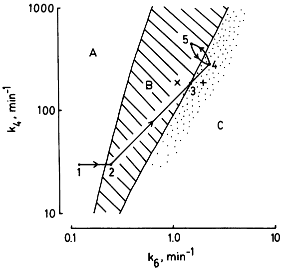
Satisfaction degree $sd(T,\phi) = \frac{1}{1+vd(T,\phi)} \in [0,1]$

Satisfaction Landscape for Parameter Optimization

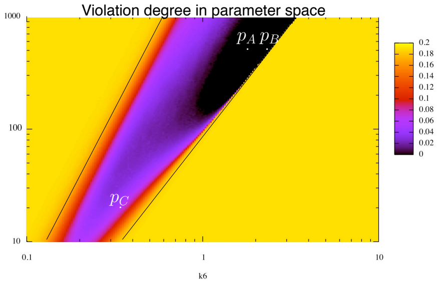
Example with :

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

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



Bifurcation diagram



LTL satisfaction diagram

Robustness Measure Definition

Robustness defined with respect to :

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

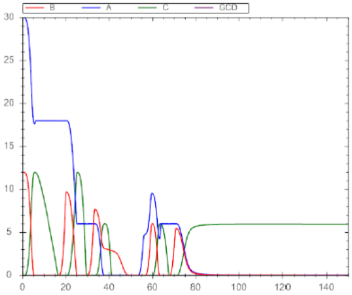
- Computational measure of robustness w.r.t. LTL($\mathbb{R}$) spec:

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

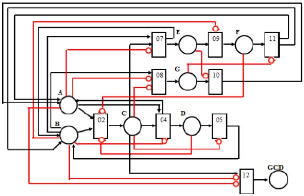
where $T(p)$ is the trace obtained by numerical integration of the ODE for perturbation p

Digital/Analog Computation with Reaction Rates

```
GreatestCommonDivisor(A, B)
begin
    while A ≠ B
        if A > B
            A := A − B
        else if B > A
            swap(A, B)
    GCD := A
end
```



	Main Reactions	Preconditions
01	while $[A] \neq [B]$	
02	$(A + B \to C)$	$\neg D_\theta \wedge \neg F_\theta$
03	if $[A] > [B]$	
04	$C \to D$	$A_\theta \wedge \neg B_\theta$
05	$D \to B$	$\neg C_\theta$
06	else if $[B] > [A]$	
07	$C \to E$	$\neg A_\theta \wedge B_\theta$
08	$B \to G$	$\neg C_\theta \wedge \neg A_\theta$
09	$E \to F$	$\neg B_\theta$
10	$G \to A$	$\neg E_\theta$
11	$F \to A + B$	$\neg G_\theta$
12	$C \to GCD$	$\neg A_\theta \wedge \neg B_\theta$



Purely Analog Characterization of Ptime [Pouly Bournez Graca 2015])

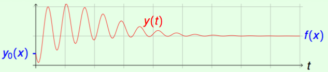
Shannon's General Purpose Analog Circuit (GPAC)

Definition

f is **poly-computable** by a GPAC iff $\exists p, q$ polynomials s.t. $\forall x \in \mathbb{R}$, the solution $y = (y_1, \ldots, y_d)$ of:

$$\begin{cases} y'(t) = p(y(t)) \\ y(t_0) = q(x) \end{cases}$$

Example



satisfies that:

- $\|f(x) - y_1(t)\| \leqslant e^{-\mu}$ when $t \geqslant \text{poly}(\|x\|, \mu)$
- $\|y(t)\| \leqslant \text{poly}(\|x\|, t)$

Theorem

f is poly-computable if and only if it is computable in polytime in the sense of Computable Analysis.