A Hybridisation of the Genetically Modified Hoare Logic

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Abstract

Our objective is the **identification of dynamical parameters** in gene networks. We focus on a **hybrid version of Thomas's framework** [CCBE16] in which discrete parameters are replaced by **celerities** which take real values, and whose possible values thus cannot be enumerated. Instead, we aim at extracting **constraints** from biological knowledge to reduce the range of possible values for these celerities. Our approach extends [BCR15, BCK+15], based on **Hoare logic** [Hoa69] and Dijkstra's **weakest precondition calculus** [Dij75], where biological traces are considered as imperative programs.

1) Hybrid Thomas Framework [CCBE16]

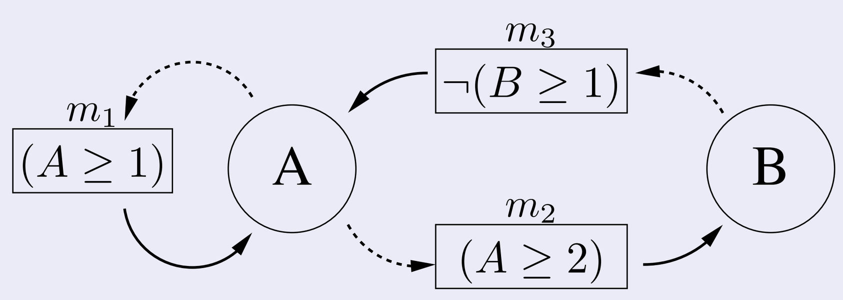

Figure 1: The gene network controlling the *lacI* repressor regulation of the lactose operon in *E. Coli*.

∗ Discrete parameters $k_{v,\omega} \in \mathbb{N}$ are replaced by **celerities** $C_{v,\omega,n} \in \mathbb{R}$, with v a variable, ω a set of resources of v and n a discrete level of v.

∗ A state $h = (\eta, \pi)$ is made of a **discrete part** η and a **fractional part** π.

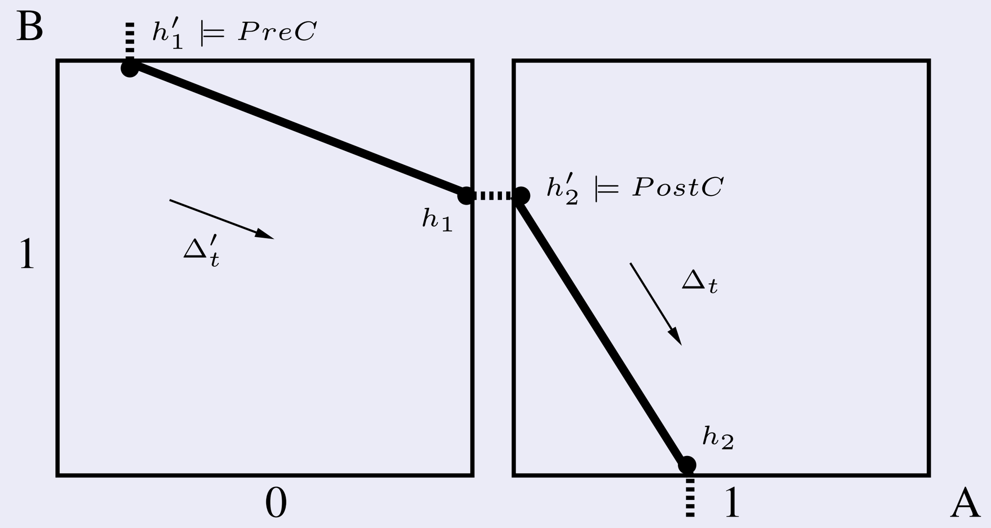

Figure 2: Example of a hybrid path containing a alternation of continuous transitions (e.g., $h'_1 \to h_1$) and discrete transitions (e.g., $h_1 \to h'_2$).

Inside each discrete state, a linear (continuous) behavior takes place, determining which variable can change its discrete level first.

2) Hoare Logic [Hoa69]

Hoare logic consists of Hoare triples:

$$\{Pre\}\ p\ \{Post\}$$

with Pre, $Post$ two propositions and p an imperative program.
Meaning: **If Pre is true before the execution of p, then $Post$ will be true after the execution of p.**

Syntax in the case of hybrid regulatory networks:

∗ **Properties** Pre and $Post$ are couples (D, H) where D is a proposition only on the discrete parts and H is a proposition on fractional parts and celerities.

∗ The **imperative program** p is a succession of triples $(\Delta t, assert, v+/-)$ representing the successive behaviors inside each discrete state:

- Δt is the time spent in the state,
- $assert$ is a set of assertions on the dynamics (slides modeling saturations),
- The discrete part of the instruction if either $v+$ or $v-$, with v a variable.

Semantics of an instruction $(\Delta t, assert, v+)$:

∗ One **continuous transition** that lasts Δt and respects $assert$.

∗ One **discrete transition** (e.g., $v+$) towards the next discrete state.

3) Weakest Precondition Calculus

We compute the **weakest precondition** of a Hoare triple to infer constraints on the model: $\mathsf{WP}(p, Post) \equiv (D', H')$.
If $p = (\Delta t, assert, v+)$ and $Post = (D, H)$, then:

- $D' \equiv D[\eta_v \backslash \eta_v + 1]$ and
- $H' \equiv H \wedge \Phi_v^+(\Delta t) \wedge \neg \mathcal{W}_v^+ \wedge \mathcal{F}_v(\Delta t) \wedge \mathcal{A}(\Delta t) \wedge \mathcal{J}_v$ where:

∗ $\Phi_v^+(\Delta t)$: v increases its fractional part up to the threshold;
∗ $\neg \mathcal{W}_v^+$: no celerities prevent v to increase its qualitative state;
∗ $\mathcal{F}_v(\Delta t)$: v is the first to reach its threshold and cross it;
∗ $\mathcal{A}(\Delta t)$: constraints given by $assert$;
∗ $\mathcal{J}_v$: junction between the fractional parts of two successive states.

4) Example: Controlling the *lacI* Repressor by *NRIp*

Application to the model of **Figure 1**:

$$\left\{\begin{matrix} D_0 \\ H_0 \end{matrix}\right\} \begin{pmatrix} T_1 \\ \top \\ B+ \end{pmatrix} ; \begin{pmatrix} T_2 \\ \mathsf{slide}^+(B) \\ A- \end{pmatrix} ; \begin{pmatrix} T_3 \\ \top \\ B- \end{pmatrix} ; \begin{pmatrix} T_4 \\ \top \\ A+ \end{pmatrix} \left\{\begin{matrix} D_4 \equiv (\eta_A = 2 \wedge \eta_B = 0) \\ H_4 \equiv \top \end{matrix}\right\}$$

$\uparrow D_1, H_1 \qquad \uparrow D_2, H_2 \qquad \uparrow D_3, H_3$

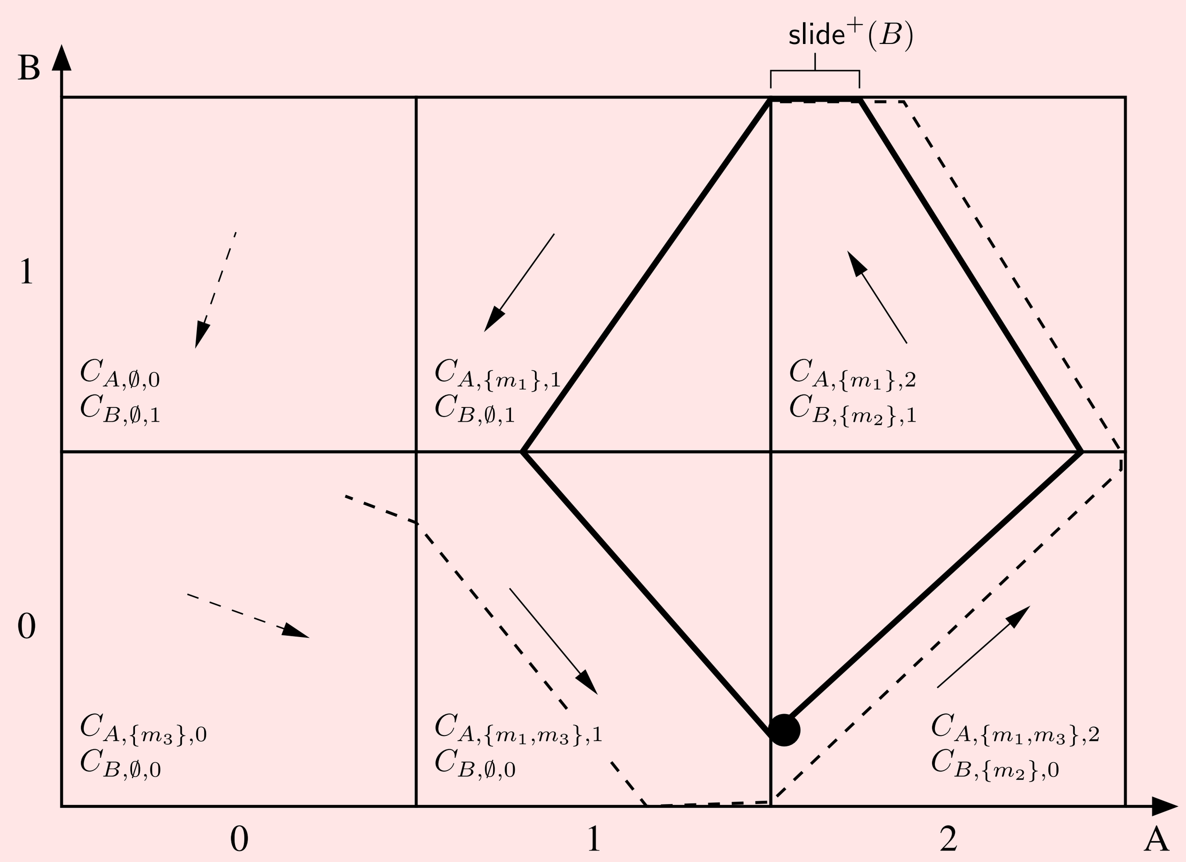

Figure 3: A limit cycle with a slide permitted by the Hoare triple above.

First step of the backward strategy: $(D_3, H_3) \equiv \mathsf{WP}((T_4, \top, A+), (D_4, H_4))$

$$\left\{\begin{matrix} D_3 \equiv (\eta_A = 1 \wedge \eta_B = 0) \\ H_3 \end{matrix}\right\} \begin{pmatrix} T_4 \\ \top \\ A+ \end{pmatrix} \left\{\begin{matrix} D_4 \equiv (\eta_A = 2 \wedge \eta_B = 0) \\ H_4 \equiv \top \end{matrix}\right\}$$

$$H_3 \equiv \Big(\neg(C_{B,\emptyset,0} > 0) \vee \neg(\pi'_{B_1} > \pi'_{B_0} - C_{B,\emptyset,0} \cdot T_1)\Big) \wedge (C_{A,\{m_1,m_3\},1} > 0) \wedge (\pi'_{A_1} = 1 - C_{A,\{m_1,m_3\},1} \cdot T_1) \wedge (\pi'_{A_0} = 0)$$

…And so on for H_2, H_1 and H_0. In the end, H_0 contains **at least one constraint for each celerity and fractional part**.

5) Example: Application to the Cell Cycle [BCB+16]

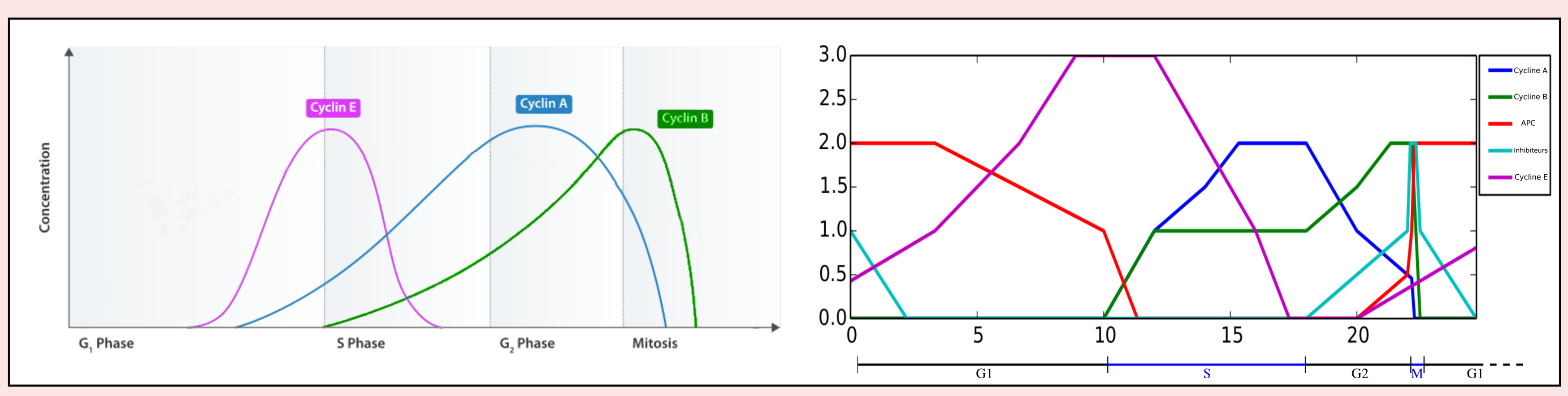

Figure 4: Left: Results from biological experiments. **Right:** Simulation using **arbitrary parameters respecting the constraints** produced by the weakest precondition calculus of our Hoare logic method.

The **robustness** of our formalism is demonstrated when comparing both figures and biological knowledge not detailed here.

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