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, BCK15], 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 $k_{\nu}$, $\nu \in \mathbb{N}$ are replaced by celerities $C_{\nu,\omega,n} \in \mathbb{R}$, with $\nu$ a variable, $\omega$ a set of resources of $\nu$ and $n$ a discrete level of $\nu$.
• A state $h = (\eta, \pi)$ is made of a discrete part $\eta$ and a fractional part $\pi$.

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:

$$\{ \text{Pre} \} \quad p \quad \{ \text{Post} \}$$

with $\text{Pre}$, $\text{Post}$ two propositions and $p$ an imperative program.

Meaning: If $\text{Pre}$ is true before the execution of $p$, then $\text{Post}$ will be true after the execution of $p$.

Syntax in the case of hybrid regulatory networks:

• Properties $\text{Pre}$ and $\text{Post}$ 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:
  • $\Delta t$ 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 $\Delta t$ 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: $WP(p, Post) \equiv \{D', H'\}$. If $p = (\Delta t, assert, v+)$ and $Post = (D, H)$, then:

• $D' \equiv D[\eta|h|0 + 1]$
• $H' \equiv H \land \Phi^+_{\Delta t}(\Delta t) \land \neg W^+ \land F_\Delta(\Delta t) \land A(\Delta t) \land J^+_v$

where:

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

4) Example: Controlling the lacI Repressor by NRIp

Application to the model of Figure 1:

$$\{D_0 \quad H_0\} \supseteq WP((T_1 \land A+), (D_1, H_1))$$

First step of the backward strategy: $(D_3, H_3) \equiv WP((T_1 \land A+) + (D_1, H_4))$

$$D_3 \equiv (\eta_A = 1 \land \eta_B = 0) \quad \{T_4 \land +\} \quad D_4 \equiv \{\eta_A = 2 \land \eta_B = 0\}$$

$H_3 \equiv H_4 \equiv T$

$H_1 \equiv$ 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.

References


