On the Analysis of Numerical Data Time Series in Temporal Logic

François Fages, Aurelien Rizk

November 18, 2007

Plan

- Introduction
- LTL with contraints
- LTL constraint solving problem
- LTL constraint solving algorithm
- Biologically relevant patterns
- Discussion

Introduction

- Logical paradigm for systems biology

$$\textit{Biological model} = \textit{Transition system}$$
$$\textit{Biological property} = \textit{Temporal logic formula}$$
$$\textit{Biological validation} = \textit{Model checking}$$

- Implemented in Biological Abstract Machine BIOCHAM
- The goal is to extract biological properties from experimental data

Kripke structures

- Kripke structure is a triplet (S, R, L), where S is a set of states, $R \subseteq R \times R$ is a transition relation and L is a labeling function.
- state: a vector of molecule concentrations
- transitions between two consecutive time points
- atomic propositions: constraints on molecular concentrations and their derivatives
- traces have the form $< t_i, x_i, dx_i/dt, d^2x_i/dt^2 >$
- the step size $t_{i+1} - t_i$ is not constant

Constraint LTL syntax

$$
\begin{aligned}
C-ltl = \; & Atom \;\mid\; F(C-ltl) \\
& \mid G(C-ltl) \;\mid\; X(C-ltl) \\
& \mid (C-ltl)U(C-ltl) \;\mid\; (C-ltl) \wedge (C-ltl) \\
& \mid (C-ltl) \vee (C-ltl) \;\mid\; (C-ltl) \Rightarrow (C-ltl) \\
& \mid not(C-ltl)
\end{aligned}
$$

$$
Atom = Value\ Op\ Variable \;\mid\; Value\ Op\ Value
$$

$$
Op = < \mid > \mid \leq \mid \geq
$$

$$
\begin{aligned}
Value = \; & float \mid [molecule] \mid d[molecule]/dt \mid d^2[molecule]/dt^2 \\
& \mid Value + Value \mid Value - Value \mid -Value \\
& Value \times Value \mid Value/Value \mid Value^{Value}
\end{aligned}
$$

LTL with constraints – examples

- $F([A] > 10)$
- $G([A] + [B] < [C])$
- $F(d[M]/dt > 0 \wedge F((d[M]/dt < 0) \wedge F(d[M]/dt > 0)))$

LTL constraint solving problem

- Given a trace T and a C-LTL formula ϕ with n variables, the *constraint solving problem* $\exists v \in \mathbb{R}^n$ such that $(\phi(v))$ is the problem of determining the valuation v of the variables for which ϕ is true in T.
- In other words, we look for the domain of validity $\mathcal{D}_\phi \subset \mathbb{R}^n$ such that $T \models_{LTL} \forall v \in \mathcal{D}_\phi(\phi(v))$.

LTL constraint solving algorithm

- starting from the end of the trace, label each time point t_i by the subformula $F\psi$ (resp. $G\psi$,, resp. $\psi_1 U \psi_2$) and its domain of validity $\mathcal{D}_{F\psi}(t_i) = \mathcal{D}_{F\psi}(t_{i+1}) \cup \mathcal{D}_{\psi}(t_i)$,
  resp. $\mathcal{D}_{G\psi}(t_i) = \mathcal{D}_{G\psi}(t_{i+1} \cap \mathcal{D}_{\psi}(t_i))$,
  resp. $\mathcal{D}_{\psi_1 U \psi_2}(t_i) = \mathcal{D}_{\psi_2}(t_i) \cup (\mathcal{D}_{\psi_1 U \psi_2}(t_{i+1}) \cap \mathcal{D}_{\psi_1}(t_i))$
- label each time point t_i by the subformula $X\psi$ (resp. $\psi_1 \wedge \psi_2$, resp. $\psi_1 \vee \psi_2$) and its domain of validity $\mathcal{D}_{X\psi}(t_i) = \mathcal{D}_{\psi}(t_{i+1})$,
  resp. $\mathcal{D}_{\psi_1 \wedge \psi_2}(t_i) = \mathcal{D}_{\psi_1}(t_i) \cap \mathcal{D}_{\psi_\in}(t_i)$,
  resp. $\mathcal{D}_{\psi_1 \vee \psi_2}(t_i) = \mathcal{D}_{\psi_1}(t_i) \cup \mathcal{D}_{\psi_2}(t_i)$
- return the non-empty domain $\mathcal{D}_{\psi}(t_i)$ for all time points t_i

Properties of the algorithm

- The algorithm is correct and complete: a valuation v makes ψ true at time t_i, $T, t_i \models_{LTL} (\psi(v))$ iff v is in the computed domain of ψ at $t_i, v \in \mathcal{D}_\psi(t_i)$.
- time complexity: $O(kn^{dv+1})$, where k, d, v are respectively the size, the depth and the number of variables of the C-LTL formula and n is the size of the trace.

Biologically relevant patterns

- *Reachability:* $F([A] \geq p)$
- *Stability:* $G([A] \leq p_1 \wedge [A] \geq p_2)$: what is the range of values of [A]
- *Oscillation:* $F((d[A]/dt > 0 \wedge [A] > v_1) \wedge F(d[A]/dt < 0 \wedge [A] < v_2))$: what amplitude $(v_1 - v_2)$ in at least one oscillation?
- *Influence:* $G(d[A]/dt \geq p_1 \Rightarrow d^2[B]/dt^2 \geq 0)$: above which treshold has A influence on B?

Discussion

Thank you for you attention.
Questions?