Trace Simplications preserving Temporal Logic Formulae with Case Study in a Coupled Model of the Cell Cycle and the Circadian Clock

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Inria
Experimental observations on periods and phases suggest bidirectional influence between cell divisions and the autonomous cellular circadian clock.

**Context:** Optimizing cancer treatment with chronotherapy

- **Model building** assisted with formal methods (model calibration)
- **Predictions:** mechanisms and perturbations, optimization

**Bidirectional coupled model** of the cell cycle and the circadian clock

What are the mechanisms behind these observations?
Temporal logic specifications

- **Dynamical behaviors for oscillatory systems:**
  - period, amplitude, phase
  - oscillations regularity

- **Formalised with temporal logic:**
  Ex: \( \text{period } \phi = \exists (t1, t2) \mid p = t2 - t1 \land t1 < t2 \)
  \[ \land \mathbf{F}( \frac{dA}{dt} > 0 \land \mathbf{X}( \frac{dA}{dt} \leq 0 \land Time = t1)) \]
  \[ \land \mathbf{F}( \frac{dA}{dt} > 0 \land \mathbf{X}( \frac{dA}{dt} \leq 0 \land Time = t2)) \]

- **Applications:**
  - **Data analysis:** extracting meaningful information from a trace
  - **Model checking:** verifying that a model satisfies some constraints
  - **Model analysis:** comparing how the properties of a model evolve when some parameters vary
  - **Parameter inference:** continuous satisfaction degree of a temporal logic formula, powerful optimization algorithm **CMA-ES**

http://lifeware.inria.fr/Biocham/
Generic algorithm:

- **Decomposition** of $\phi$ in sub-formulas
- For each constraint and each time point, computing of a **domain** of possible variables
- **Combination** of the subdomains with the logical operators:
  - Operator $F$ (finally) $\rightarrow$ union: $D_{s_i}^T, F_\phi = \bigcup_{j=i}^{n} D_{s_j}^T, \phi$
  - Operator $G$ (globally) $\rightarrow$ intersection: $D_{s_i}^T, G_\phi = \bigcap_{j=i}^{n} D_{s_j}^T, \phi$
  - Operator $X$ (next) $\rightarrow$ next domain if valid: $D_{s_i}^T, X_\phi = D_{s_{i+1}}^T, \phi$
  - Operator $U$ (until) $\rightarrow$ union of intersections: $D_{s_i}^T, \phi U_\psi = \bigcup_{j=i}^{n} (D_{s_j}^T, \psi \cap \bigcap_{k=i}^{j-1} D_{s_k}^T, \phi)$
- Domain for $\phi =$ combined domain for the **first point** of the trace

\[ \phi = F([A] > s) \]
\[ D_\phi = \{ s < \text{max}[A] \} \]

**Computational cost:** up to $O(n^\nu)$
($\nu =$ number of variables)

How to find a simplified trace that will keep the same validity domain?
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(\( v = \) number of variables)

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Validation domain computing algorithm

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  - Operator $U$ (until) $\rightarrow$ union of intersections: $D_{s_i,\phi U \psi}^T = \bigcup_{j=i}^n (D_{s_j,\psi}^T \cap \bigcap_{k=i}^{j-1} D_{s_k,\phi}^T)$
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  - Operator \( \mathbf{F} \) (finally) \( \rightarrow \union \):
    \[ \mathcal{D}_{s_i}^{T} \mathbf{F} \phi = \bigcup_{j=i}^{n} \mathcal{D}_{s_j}^{T} \phi \]
  - Operator \( \mathbf{G} \) (globally) \( \rightarrow \intersection \):
    \[ \mathcal{D}_{s_i}^{T} \mathbf{G} \phi = \bigcap_{j=i}^{n} \mathcal{D}_{s_j}^{T} \phi \]
  - Operator \( \mathbf{X} \) (next) \( \rightarrow \) next domain if valid:
    \[ \mathcal{D}_{s_i}^{T} \mathbf{X} \phi = \mathcal{D}_{s_{i+1}}^{T} \phi \]
  - Operator \( \mathbf{U} \) (until) \( \rightarrow \) union of intersections:
    \[ \mathcal{D}_{s_i}^{T} \phi \mathbf{U} \psi = \bigcup_{j=i}^{n} (\mathcal{D}_{s_j}^{T} \psi \cap \bigcap_{k=i}^{j-1} \mathcal{D}_{s_k}^{T} \phi) \]
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**Computational cost:** up to \( O(n^v) \) 
\( (v = \text{number of variables}) \)

How to find a simplified trace that will keep the same validity domain?
Dedicated solvers:

- Specific function
Trace simplification

For the case when there is no dedicated solver, how to make the generic algorithm more efficient?

Trace simplification: local extrema

Under which condition on the constraints is it safe to use this simplification?
Proof of validity: peak and period

**Peak**

**Formula:** \( \phi = F(\frac{dA}{dt} > 0 \land X(\frac{dA}{dt} \leq 0 \land Time = t)) \)

**Validity Domain:**

\[ D_{T, \phi} = D_{s_0, \phi} \]

\[ = \bigcup_{i=0}^{n} (D_{s_i}^{T}, \frac{dA}{dt} > 0) \cap (D_{s_{i+1}}^{T}, \frac{dA}{dt} \leq 0) \cap (D_{s_{i+1}}^{T}, Time = t) \]

\[ = \bigcup_{i \in \{0, \ldots, n\}} D_{s_{i+1}}^{T}, Time = t \]

\[ = \bigcup_{i \in \{0, \ldots, n\}} \{Time_{s_{i+1}} \} \]

**Trace simplification:**

The optimal trace simplification is \( T_J \) with \( J = \{i, i+1 \in \{0, \ldots, n\} | \frac{dA}{dt}_s > 0 \land \frac{dA}{dt}_{s+1} \leq 0 \} \)

\( T_s^A \) is a simplification of \( T \) for \( \phi \).

**Period**

**Formula:** \( \phi = \exists(t_1, t2) | p = t_2 - t_1 \land t_1 < t_2 \)

\[ \land F(\frac{dA}{dt} > 0 \land X(\frac{dA}{dt} \leq 0 \land Time = t1)) \]

\[ \land F(\frac{dA}{dt} > 0 \land X(\frac{dA}{dt} \leq 0 \land Time = t2)) \]

\[ \land \neg \exists t_3 | t_1 < t_3 < t_2 \land F(\frac{dA}{dt} > 0 \land X(\frac{dA}{dt} \leq 0 \land Time = t3)) \]
Proof of validity: peak and period

Peak

**Formula:** $\phi = F\left(\frac{dA}{dt} > 0 \land X\left(\frac{dA}{dt} \leq 0 \land Time = t\right)\right)$

**Validity Domain:**

$D_{T,\phi} = D_{s_0,\phi}^T$

$$= \bigcup_{i=0}^{n} \left( D_{s_i, \frac{dA}{dt} > 0}^T \cap \left( D_{s_{i+1}, \frac{dA}{dt} \leq 0}^T \cap D_{s_{i+1}, Time = t}^T \right) \right)$$

$$= \bigcup_{i \in \{0, \ldots, n\}} \{ Time_{s_{i+1}} \}$$

**Proof of validity:**

The optimal trace simplification is $T_e^e_A$ with $J = \{ i, i + 1 \in \{0, \ldots, n\} \mid \frac{dA}{dt}_{s_i} > 0 \land \frac{dA}{dt}_{s_{i+1}} \leq 0 \}$

$T_e^e_A$ is a simplification of $T$ for $\phi$.

Period

**Formula:** $\phi = \exists(t1, t2) \mid p = t_2 - t_1 \land t_1 < t_2$

$$\land F\left(\frac{dA}{dt} > 0 \land X\left(\frac{dA}{dt} \leq 0 \land Time = t1\right)\right)$$

$$\land F\left(\frac{dA}{dt} > 0 \land X\left(\frac{dA}{dt} \leq 0 \land Time = t2\right)\right)$$

$$\land \neg \exists t_3 \mid t_1 < t_3 < t_2 \land F\left(\frac{dA}{dt} > 0 \land X\left(\frac{dA}{dt} \leq 0 \land Time = t3\right)\right)$$

Same trace simplification
Proof of validity: phase and amplitude

Peak

Formula:
\[ \phi = \exists (t_1, t_2) \mid p = t_2 - t_1 \land t_1 < t_2 \]
\[ \land F \left( \frac{dA}{dt} > 0 \land X \left( \frac{dA}{dt} \leq 0 \land \text{Time} = t_1 \right) \right) \]
\[ \land F \left( \frac{dB}{dt} > 0 \land X \left( \frac{dB}{dt} \leq 0 \land \text{Time} = t_2 \right) \right) \]

Trace simplification:
The optimal trace simplification is \( T_J \) with \( J = \{ i, i + 1 \in \{ 0, \ldots, n \} \} \)
\[ \frac{dA}{dt} s_i > 0 \land \frac{dA}{dt} s_{i+1} \leq 0 \]

\( T_{eA,B} \) is a simplification of \( T \) for \( \phi \).

Minimal amplitude

Formula: \( \phi = \exists v \mid F(A < v) \land F(A > v + a) \)

Validity Domain:
\[ D_{T,\phi} = \Pi_a (D_{s_0}^T, F(A < v) \cap D_{s_0}^T, F(A > v + a)) \]
\[ = \Pi_a (\bigcup_{i=0}^{n} D_{s_i}^T, A < v) \cap \bigcup_{i=0}^{n} D_{s_j}^T, A > v + a)) \]
\[ = \Pi_a (D_{s_{\min A}}^T, A < v \cap D_{s_{\max A}}^T, A > v + a) \]

Trace simplification:
The optimal trace simplification is \( T_J \) where \( J = \{ \min A, \max A \} \).
\( T_{eA} \) is a simplification of \( T \) for \( \phi \).
General Theorems

**First theorem:** If a simplification trace is correct for $\phi$ and $\psi$ then it is correct for the logical combinations of $\phi$ and $\psi$.

**Proof:** $D_{s_i, \phi \land \psi}^T = D_{s_i, \phi}^T \cap D_{s_i, \psi}^T = D_{s_j, \phi}^T \cap D_{s_j, \psi}^T = D_{s_j, \phi \land \psi}^T$

**Second theorem:**
If a subtrace contains extreme domains, it is a simplification for $F$.

**Proof:** $D_{\phi}^T = U_i D_{s_j, \phi} \cap U_j D_{s_j, \phi}$

Similar result for $G$: A simplification trace of $G\phi$ is the set of points $s_j$ whose $D_{s_j, \phi}$ is contained in all the $D_{s_i, \phi}$

**Corollary:** A simplified trace on $T$ for $F(c \land \phi)$ can be found by discarding all the points where $c$ is false, if this defines a simplified trace on $T$ for $\phi$. 
First theorem: If a simplification trace is correct for \( \phi \) and \( \psi \) then it is correct for the logical combinations of \( \phi \) and \( \psi \).

Proof: 

\[
D_{s_i, \phi \land \psi}^T = D_{s_i, \phi}^T \cap D_{s_i, \psi}^T = D_{s_j, \phi}^T \cap D_{s_j, \psi}^T = D_{s_j, \phi \land \psi}^T
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Second theorem:
If a subtrace contains extreme domains, it is a simplification for $F$.

**Proof:**

$$D_{T,\phi} = \bigcup_i D_{s_i,\phi} \cap \bigcup_j D_{s_j,\phi}$$

Similar result for $G$: A simplification trace of $G\phi$ is the set of points $s_j$ whose $D_{s_j,\phi}$ is contained in all the $D_{s_i,\phi}$.
Second theorem
**Corollary:** A simplified trace on $T$ for $F(c \land \phi)$ can be found by discarding all the points where $c$ is false, if this defines a simplified trace on $T$ for $\phi$.

**Formula:**

$$\phi = F(\text{Time} > 20 \land A < v)$$

$$D_{T, \phi} = D_{s_0, F(\text{Time} > 20 \land A < v)}$$

$$= \bigcup_{i=0}^{n} D_{s_i, \text{Time} > 20 \land A < v}$$

$$= \bigcup_{i=0}^{n} (D_{s_i, \text{Time} > 20} \cap D_{s_i, A < v})$$

$$= \bigcup \{D_{s_i, A < v} \mid \text{Time}_{s_i} > 20 \}$$

$$= D_{s_{\text{min} A > 20}, A < v}$$

**Trace simplification:**

The single point $s_{\text{min} A > 20}$ defines an optimal trace simplification of $T$ for $\phi$.

$T^e_A$ is not a simplification of $T$ for $\phi$ unless it does contain a local minimum such that $\text{Time} > 20$. 
**Corollary:** A simplified trace on $T$ for $F(c \land \phi)$ can be found by discarding all the points where $c$ is false, if this defines a simplified trace on $T$ for $\phi$.

**Formula:**

$$\phi = F(\text{Time} > 20 \land A < v)$$

$$D_{T, \phi} = D_{s_0, F(\text{Time} > 20 \land A < v)}$$

$$= \bigcup_{i=0}^{n} D_{s_i, \text{Time} > 20 \land A < v}$$

$$= \bigcup_{i=0}^{n} \left( D_{s_i, \text{Time} > 20} \cap D_{s_i, A < v} \right)$$

$$= \bigcup \left\{ D_{s_i, A < v} \right\} \{i \mid \text{Time}_{s_i} > 20\}$$

$$= D_{s_{\min A > 20}, A < v}$$

**Trace simplification:**

The single point $s_{\min A > 20}$ defines an optimal trace simplification of $T$ for $\phi$. $T^c_A$ is not a simplification of $T$ for $\varphi$ unless it does contain a local minimum such that $\text{Time} > 20$. 

**Threshold**

![Graph showing trace simplification](image)
Corollary: A simplified trace on $T$ for $F(c \land \phi)$ can be found by discarding all the points where $c$ is false, if this defines a simplified trace on $T$ for $\phi$.

**Trace simplification:**
The single point $s_{\min A \geq 20}$ defines an optimal trace simplification of $T$ for $\phi$. $T^e_A$ is not a simplification of $T$ for $\phi$ unless it does contain a local minimum such that $\text{Time} > 20$. 
**Corollary:** A simplified trace on $T$ for $F(c \land \phi)$ can be found by discarding all the points where $c$ is false, if this defines a simplified trace on $T$ for $\phi$. 

**Formula:**

$\phi = F(\text{Time} \geq 20 \land A < V)$

$D_{T, \phi} = D_{s_0, F(\text{Time} \geq 20 \land A < V)}$

$= \bigcup_{i=0}^{n} D_{s_i, \text{Time} > 20 \land A < V}$

$= \bigcup_{i=0}^{n} (D_{s_i, \text{Time} > 20} \cap D_{s_i, A < V})$

$= \bigcup \{D_{s_i, A < V} \mid \text{Time}_{s_i} > 20\}$

$= D_{s_{\min A > 20}, A < V}$

**Threshold**

**Trace simplification:** The single point $s_{\min A > 20}$ defines an optimal trace simplification of $T$ for $\phi$. $T_{e_A}$ is not a simplification of $T$ for $\phi$ unless it does contain a local minimum such that $\text{Time} > 20$. 

**Diagram:**

- A vs V graph with time axis and a threshold at $\text{Time}=20$.
- A simplified trace $s_{\min A > 20}$ is marked on the graph.
Crossing

Formula: $\phi = F(A > B \land X(A \leq B \land Time = t))$

Validity Domain:

$$\bigcup_{i=0}^{n} \{ T_{e,B}^i \}$$

Here $T_{e,A,B}^i$ is NOT a simplification of $T$ for $\phi$.

A simplification trace is defined by the points in:

$$J = \{ i, i+1 \in \{ 0, \ldots, n \} | A_{s_i} > B_{s_i} \land A_{s_{i+1}} \leq B_{s_{i+1}} \}$$
**Crossing**

**Formula:** \( \phi = F(A > B \land X(A \leq B \land Time = t)) \)

**Validity Domain:**

\[
\bigcup_{i=0}^{n} \left\{ A_{s_i} > B_{s_i} \land \left( A_{s_i+1} \leq B_{s_i+1} \land \bigcup_{i=0}^{n} \{ \text{Times}_{s_{i+1}} \} \right) \right\}
\]

Here \( T_{A,B}^r \) is NOT a simplification of \( T \) for \( \phi \).

A simplification trace is defined by the points in:

\[
J = \{ i, i + 1 \in \{0, \ldots, n\} \mid A_{s_i} > B_{s_i} \land A_{s_{i+1}} \leq B_{s_{i+1}} \}
\]
Evaluation on Oscillation Constraints between the Cell Cycle and Circadian Clock

- The cell cycle and the circadian clock: two coupled oscillators involving:
  - qualitative properties: oscillations, stability
  - quantitative properties: period of each oscillator, phase

- Constraints on one molecule:
  - Minimum amplitude
  - Distance between successive peaks
  - Regularity of the distances between peaks
  - Regularity of the peak amplitudes

- Constraints on two molecules:
  - Phase

Cell cycle: MPF, Wee1
Circadian clock: Bmal1, PerCry, Rev-erbα
Evaluation on Oscillation Constraints between the Cell Cycle and Circadian Clock

Trace simplification:
- **Extrema subtrace** implemented in BIOCHAM
- Computing times:
  - Rosenbrock’s variable step-size simulation: 8-16 ms
  - 4th order Runge-Kutta fixed step-size simulation: 160-250 ms

**Validity domain computing time** (in ms):

<table>
<thead>
<tr>
<th>Formula</th>
<th>Nb of points Solver</th>
<th>First trace variable</th>
<th>fixed</th>
<th>Second trace variable</th>
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</tbody>
</table>
Conclusion

• Temporal logic patterns provide an elegant way to
  o **extract meaningful information** on the periods and phases from numerical traces
  o use these formulae as **constraints for parameter search**

• Simplifying the trace prior to the solving makes the generic solving algorithm more efficient

• Under some **general conditions on the syntax of the formulae given as theorems** it is correct to keep in the trace only the time points corresponding to
  • the **local extrema** of the molecules
  • or the **crossing points** between molecular concentrations

• On simulation traces, the **speedup obtained in computation time** was by several orders of magnitude: up to 1000 fold.

• The trace simplifications described in this paper are implemented in **Biocham** release 3.6.