Signal-$\mathcal{LBC}$ and posttranslational oscillators

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Introduction

In this talk I will

- give a brief overview of the Logic of Behaviour in Context ($\mathcal{LBC}$)
- define the semantics of Signal-$\mathcal{LBC}$
  - relative time
  - efficient data structures
  - (event precision)
- show how $\mathcal{LBC}$ is being used in a biochemical case study
  - posttranslational oscillator models
  - formulae for oscillation
  - inhibitor response
  - phase response

Part I

$\mathcal{LBC}$

$\mathcal{LBC}$ recap

$\mathbf{F}\phi$	Eventually (**F**uture)
$\mathbf{G}\phi$	Always (**G**lobally)
$\mathbf{F}_{[0,t]}\phi$	Eventually within t
$\mathbf{G}_{[t,t']}\phi$	Always between t and t'
$Q \triangleright \phi$	Introducing $Q \implies \phi$
$\mathbf{G}_{[0,t]}(Q \triangleright \phi)$	At any time until t introducing $Q \implies \phi$
$\mathbf{F}_{[t,t']}(Q \triangleright \phi)$	At some time between t and t' introducing $Q \implies \phi$

Semantics of $\mathcal{LBC}$

F and **G** can be defined in terms of **U**:

$$\mathbf{F}_I \phi \equiv \top \mathbf{U}_I \phi$$
$$\mathbf{G}_I \phi \equiv \neg \mathbf{F}_I \neg \phi$$

Key rules in the semantics of $\mathcal{LBC}$:

$$P \vDash Q \triangleright \phi \iff (Q \parallel P) \vDash \phi$$
$$P \vDash \phi \mathbf{U}_I \psi \iff \exists t \in I, P(t) \vDash \psi \text{ and } \forall t' \in [0, t], P(t') \vDash \phi$$

Absolute or relative time depends on the semantics of $P(t)$:

- $P(t)$ begins at time $t \implies$ absolute
- $P(t)$ begins at time reset to zero $\implies$ relative

Absolute vs. relative

Absolute time:

- time bounds refer absolutely to the time in the model
- original efficient algorithms for $\mathcal{LBC}$ required this

Relative time:

- time bounds are relative to the parent modality
- consider $\mathbf{FG}_{[0,3]}\phi$.
- with relative time: "Eventually ϕ for at least 3 time units"
- properties like this are definitely useful for biochemistry.

The algorithmic landscape for $\mathcal{LBC}$

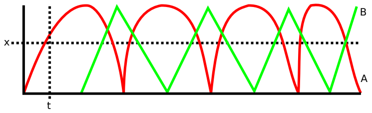
	Rel/Abs	Linear TL	Short-circuit
Naive	Both	$\times$	✓
Dynamic	Abs	✓	$\times$
Hybrid	Abs	✓	✓
Signal	Rel	✓	$\times$

Part II

Signal-$\mathcal{LBC}$

(Maler & Nickovic, 2004)

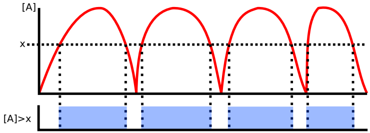
A trace (time series):

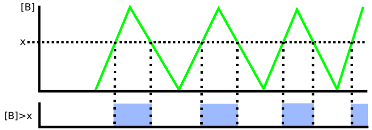


A formula:

$$\mathbf{F}_{[0,t]}((A > x) \vee (B > x))$$

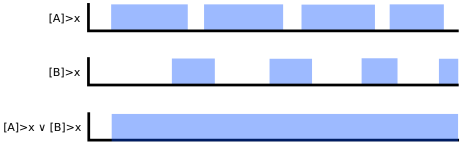
Each proposition of the formula becomes a signal:





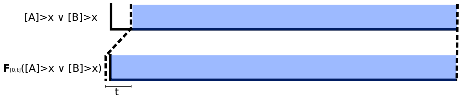
Signal combinators

$\vee$ is the union of intervals:



$\mathbf{F}_{[a,b]}$ for a signal with intervals $[m, n)$ is the "positive Minkowski difference" of each interval:

$$[m, n) \ominus [a, b] \cap \mathbb{R}_{\geq 0}$$
$$= [m - b, n - a) \cap \mathbb{R}_{\geq 0}$$

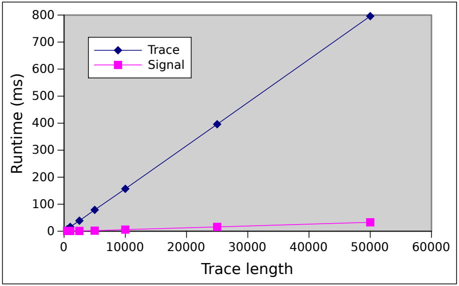


A signal for context

To compute a signal for $Q \triangleright \phi$, for now we:

- recalculate the trace at each original time-point with Q introduced
- signal represents the truth values of ϕ at each of these points
- this is essentially the same as in the old algorithms, and has the same worst-case time
- there is a better way (current work on sensitivity)

Performance



- Worst case for temporal fragment is much better!
- Worst case for full $\mathcal{LBC}$ is comparable
  - lose short-circuiting, so slower in practical terms
  - but gain more useful relative time expressiveness
  - (improvements to come here)

Key properties

Benefits of a signal semantics:

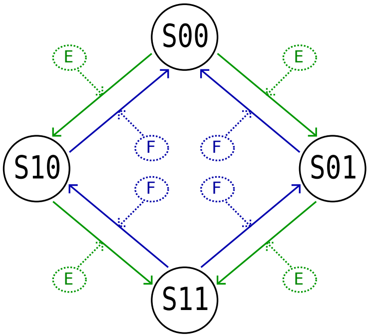
- gives an efficient relative time semantics
- actually more efficient for temporal fragment (compression)
- event detection could be used to generate signals directly
  - event precision
  - possibly even performance gain (no trace to signal conversion)

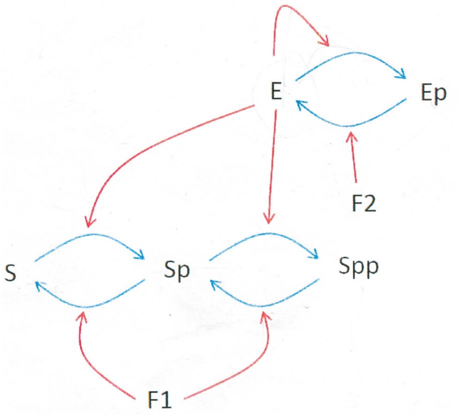
Limitations:

- doesn't readily short-circuit
- no improvement in worst-case time for full $\mathcal{LBC}$
  - dominated by solver calls

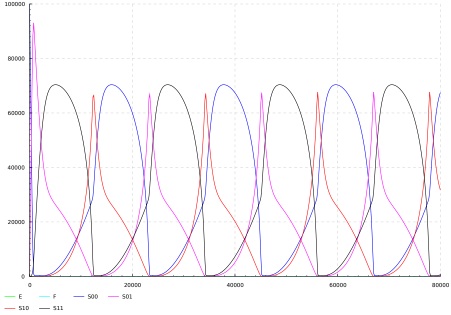
Part III

Posttranslational oscillators





- Jolley's model is candidate mechanism for a circadian PTO
- Seaton's model is novel oscillator mechanism based on auto-inhibition
- The Kai oscillator is a large, well studied model of the circadian clock mechanism in a cyanobacteria.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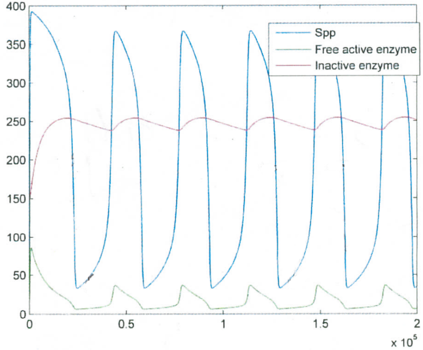
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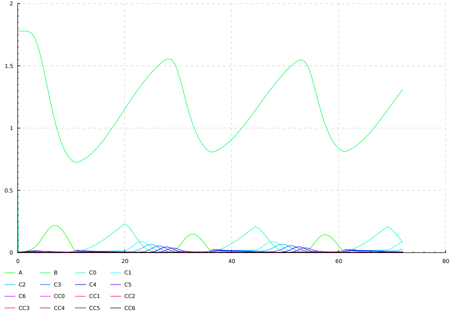
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CC4
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CC6

Case study objectives

- Behaviour of coupled oscillators
  - previous talk (coupled Jolley PTOs)
  - hard to do with ODEs, easy with a high level language
  - pairing of each of the three types
  - chain of all three
- Comparison of behaviour between models
  - circadian clock behaviour vs. conjectured mechanisms
  - comparison by results of model checking
  - oscillation, inhibitor response, and phase response

I will show a selection of some of the more interesting properties we can formulate using $\mathcal{LBC}$.

Oscillation:

$$PTO \models \mathbf{G}_{[0,t]}(\mathbf{F}_{[0,p]}(([S]' > 0) \wedge \mathbf{F}_{[0,p]}([S]' < 0)))$$

where $[S]'$ is the first derivative of $[S]$.

- until time t the concentration of S is always, within time p, increasing then decreasing within time p
- oscillation with period at most p
- suitable for these models, but not a general formula for oscillation
- susceptible to noise, but again fine for these models

$\mathcal{LBC}$ properties of PTO models

General oscillation using context:

$$PTO \models \mathbf{F}_{[p_1,p_2]}(\widehat{PTO} \triangleright (\mathbf{F}_{[0,s]}\mathbf{G}_{[0,t]}(|[S] - [\widehat{S}]| < \epsilon)))$$

where $\widehat{PTO}$ is a copy of PTO, S is the species being observed, and $\widehat{S}$ is the copy of S in $\widehat{PTO}$, and s is a maximum transient period before reaching limit cycle.

- if we introduce $\widehat{PTO}$ after some period in $[p_1, p_2]$ then, within s, $[S]$ and $[\widehat{S}]$ will synchronise to within ϵ until t.
- a very succinct description of something that is non-trivial to code in, for example, MATLAB
- checking might be computationally intensive, but gives us general oscillation

$\mathcal{LBC}$ properties of PTO models

So if $\texttt{Osc}$ is one of these oscillation properties:

$$\mathit{PTO1} \models \mathit{PTO2} \triangleright \texttt{Osc}$$

and

$$\mathit{PTO1} \models \mathbf{G}_{[0,c]}(\mathit{PTO2} \triangleright \texttt{Osc})$$

where c is the end of the first cycle of *PTO1*.

We can test that the coupled oscillators still oscillate, even when coupled in any phase.

$\mathcal{LBC}$ properties of PTO models

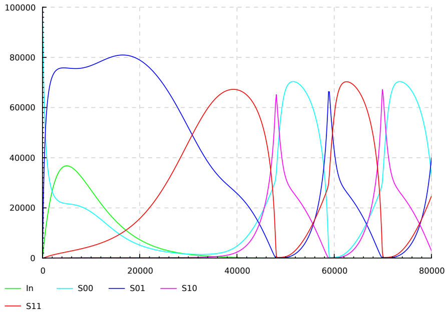
Perturbation response:

$$PTO \models \mathbf{F}_{[0,t]}(P \triangleright \mathbf{F}_{[0,r]}([S] > pk))$$

- is some peak value pk ever exceeded under some perturbation P, within time t
- r is the max expected time of the peak after perturbation

$\mathcal{LBC}$ properties of PTO models

Phase response:



- given a perturbation, at any point in the cycle, what is the effect on the phase of oscillation?
- biologists will plot a phase response curve, using a number of experiments
- but we can formulate some qualitative properties of phase response

$\mathcal{LBC}$ properties of PTO models

Phase response:

$$PTO \models \widehat{PTO} \triangleright \mathbf{F}_{[c_1,c_2]}(P \triangleright (\mathbf{G}_{[t_1,t_2]}([\widehat{S}]' > 0 \implies \mathbf{F}_{[s_1,s_2]}[S]' > 0)))$$

- some perturbation P applied within $[c_1, c_2]$ will cause a forward phase shift $\in [s_1, s_2]$
- t_1 is a known max transient period after introducing P
- t_2 is a sensible max time to simulate for
- assumes we know the perturbed system still oscillates

Conclusions

- Signal-$\mathcal{LBC}$ gives a relative time logic with reasonably efficient model checking.
- It is useful for checking biochemical properties.
- Although model checking might not be as computationally efficient as a hand-rolled solution it automates the process of implementation.
- Use of a high level language (cπ) for defining models, a rich query language ($\mathcal{LBC}$), and model checking (CPiWB) simplifies the process of analysing coupled models with complex dynamics.