Analysis of a Post-translational Oscillator using Process Algebra and Spatio-temporal Logic

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Introduction

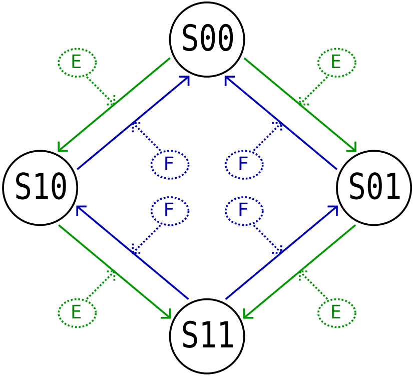
- Modelling of a theoretical post-translational oscillator (PTO);
  - Continuous π-calculus process algebra (cπ);
- To verify the theoretical model exhibits some of the properties of a circadian clock.
- Model analysis;
  - Model perturbation and time series inspection;
- Spatio-temporal model checking experiments;
  - Logic of Behaviour in Context ($\mathcal{LBC}$).

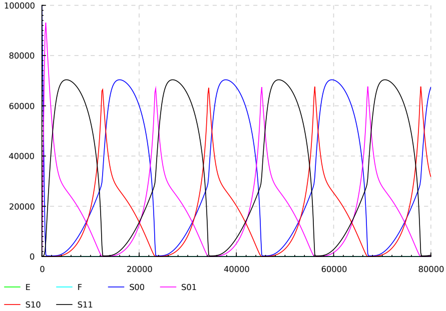
PTOs

- Purely autonomous biochemical oscillators—no regulation;
- Conjectured to be components of larger systems of oscillators/clocks;
- Circadian clocks, cell-cycle, etc.

Jolley PTO

- One substrate, four phosphorylation states, two enzymes;
- Sufficient for robust oscillatory dynamics;





- Jolley, Ode, & Ueda (2012), Cell Reports, 2(4), 938–950.

Jolley PTO

- Authors show robustness to temperature variation.
- But does it exhibit other circadian clock-like behaviour?
  - Coupling with other clocks,
  - in and out of phase;
  - Robustness under perturbation.

cπ model

$$E \triangleq e \ldots E$$
$$F \triangleq f \ldots F$$

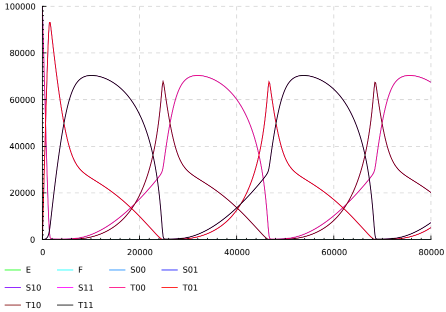
$$S00 \triangleq \ldots s00a \ldots S01 + s00b \ldots S10$$
$$S01 \triangleq \ldots s01a \ldots S11 + s01b \ldots S00$$
$$S10 \triangleq \ldots s10a \ldots S11 + s10b \ldots S00$$
$$S11 \triangleq \ldots s11a \ldots S01 + s11b \ldots S10$$

$$Aff = \{s00a \leftrightarrow e,\ s00b \leftrightarrow e,\ s01a \leftrightarrow e,\ s10a \leftrightarrow e,\ s01b \leftrightarrow f,\ s10b \leftrightarrow f,\ s11a \leftrightarrow f,\ s11b \leftrightarrow f\}$$

$$\Pi \triangleq c_S \cdot S00 \parallel c_E \cdot E \parallel c_F \cdot F$$

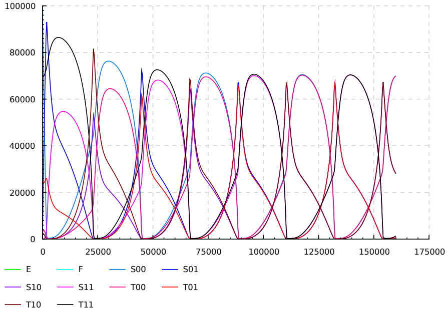
Model experiments – Coupling

- Construct new substrate T00–T11;
- Extend affinity network;
- $\Pi \triangleq c_S \cdot S00 \parallel c_T \cdot T00 \parallel c_E \cdot E \parallel c_F \cdot F$

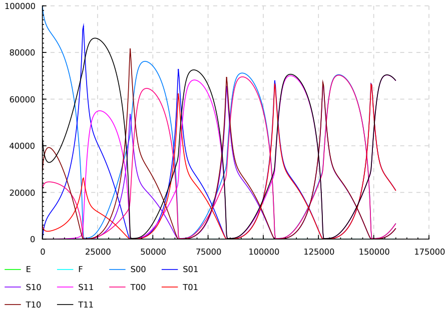


Coupling out of phase

- Run T00–T11 to quarter phase / half phase;
- Use state as initial conditions for new coupled model:



$\text{T} + \frac{1}{4}$ phase

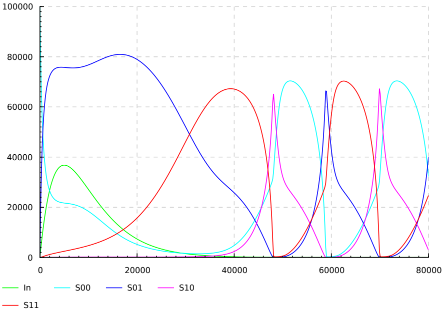


$\text{T} + \frac{1}{2}$ phase

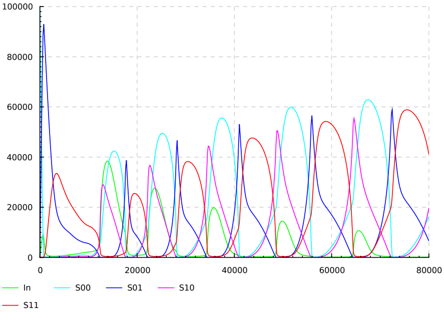
Perturbation

- Inhibitor appears in the system and decays;
- Binds to an enzyme or the substrate in some state;

$$In \triangleq ina \ldots In + \tau.0 \qquad Aff' = Aff \cup \{ina \leftrightarrow s11a\}$$
$$PIn \triangleq \tau.In$$



Binds E



Binds S11

Summary

- We have shown some specific circadian clock-like behaviour:
  - Robustness under coupling in phase;
  - and out of phase;
  - and to some perturbation.
- But these are simple cases, e.g. coupling/perturbation at some point in time...
- Does not necessarily imply coupling/perturbation robustness at *any* point in time...

Spatio-temporal model checking

- Automates the process of inspecting time series—
  - with properties of composition
  - or requiring numerous model runs.
- Can succinctly define *higher-order experiments*—
  - many models,
  - many initial conditions.

$\mathcal{LBC}$ – Basic properties

- Based on MITL:
  - $P \models \phi$
  - $P \models \mathbf{F}_{[t,t']}\phi$
  - $P \models \mathbf{G}_{[t,t']}\phi$
- With a *context modality*:
  - $P \models Q \triangleright \phi \qquad (\iff P \parallel Q \models \phi)$

$\mathcal{LBC}$ – Basic properties

- Boring examples:
  - $PTO1 \models PTO2 \triangleright \phi$
  - $PTO \models Inhib \triangleright \mathbf{F}_{[0,t]}\phi$
- A much more interesting example:
  - $PTO1 \models \mathbf{G}_{[0,t]}(PTO2 \triangleright \phi)$

Complex dynamics

- Oscillation is a difficult thing to pin down in temporal logic:
  - $PTO \models \mathbf{G}_{[0,t]}(\mathbf{F}_{[0,p]}(([S]' > 0) \wedge \mathbf{F}_{[0,p]}([S]' < 0)))$
  - $[S]'$ is the time derivative of $[S]$.
  - Describes a repeated rising and falling with period at most p,
  - but does not distinguish from noise.

Complex dynamics

- However, with $\mathcal{LBC}$ we can say:
  - $PTO \models \mathbf{F}_{[p_{min},p_{max}]}(\widehat{PTO} \triangleright (\mathbf{F}_{[0,s]}\mathbf{G}_{[0,t]}(|[S] - [\widehat{S}]| < \epsilon)))$
  - where $\widehat{PTO}$ is a copy of PTO,
  - S is the species being observed,
  - $\widehat{S}$ is the copy of S in $\widehat{PTO}$,
  - and s is a maximum transient period before reaching the limit cycle.
  - If we introduce $\widehat{PTO}$ after some period in $[p_{min}, p_{max}]$ then, within s, $[S]$ and $[\widehat{S}]$ will synchronise to within ϵ, this will happen indefinitely for at least time t.

Properties of the circadian oscillator

- Coupled oscillators still oscillate:
  - $PTO1 \models \mathbf{G}_{[0,t]}(PTO2 \triangleright \mathtt{Osc})$
  - Oscillators coupled at any time (up to t) satisfy $\mathtt{Osc}$.
- Inhibitor response:
  - $PTO \models \mathbf{G}_{[0,t]}(In \triangleright \mathbf{F}_{[0,r]}(\mathtt{Osc}))$
  - Inhibitor introduced any time (up to t) then eventually (within r) satisfies $\mathtt{Osc}$.
- Phase response:
  - $PTO \models \widehat{PTO} \triangleright \mathbf{F}_{[p_1,p_2]}(P \triangleright (\mathbf{G}_{[t_1,t_2]}([\widehat{S}]' > 0 \implies \mathbf{F}_{[s_1,s_2]}[S]' > 0)))$
  - Some perturbation P applied within $[p_1, p_2]$ will cause a *forward* phase shift in $[s_1, s_2]$.

Results

- Previous examples (and more) applied to PTO model;
- All tests pass, confirming robust circadian-like behaviour—see paper for parameters.
- Executed in the CPiWB model checker:
  - efficient STL-based implementation;
  - even the most complex examples take no longer than an overnight run;
  - Haskell implementation of logic, GNU Octave for ODE solving.

Conclusion

- We have shown:
  - Some of the benefits of using a high-level model description—
    - for simple editing and perturbation
    - and modular compositions of models.
  - A language ($\mathcal{LBC}$) for precise and succinct specification of:
    - complex properties of oscillatory dynamics;
    - *higher-order experiments*—model checking experiments with large numbers of runs and time series analysed for complex properties.