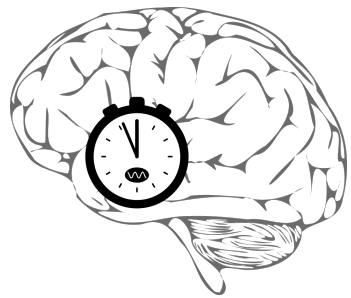
Parametric Timed Petri Net of the Mammalian Circadian Clock

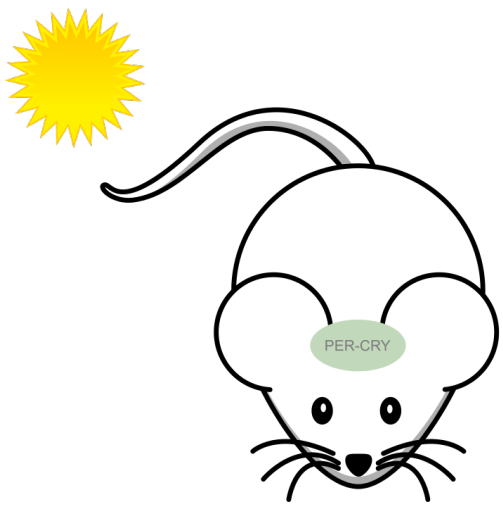
Alexander Andreychenko, Morgan Magnin, Katsumi Inoue

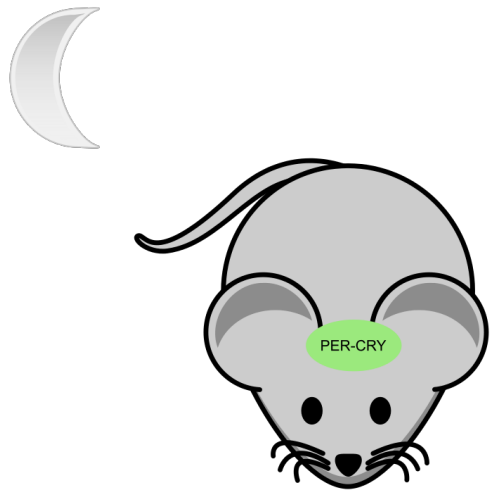
September 18, 2015



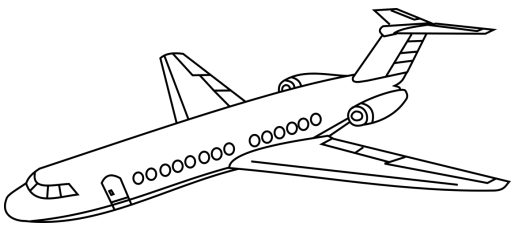
What biological systems?

Biological systems that possess the oscillatory behavior.





Motivation: health issues

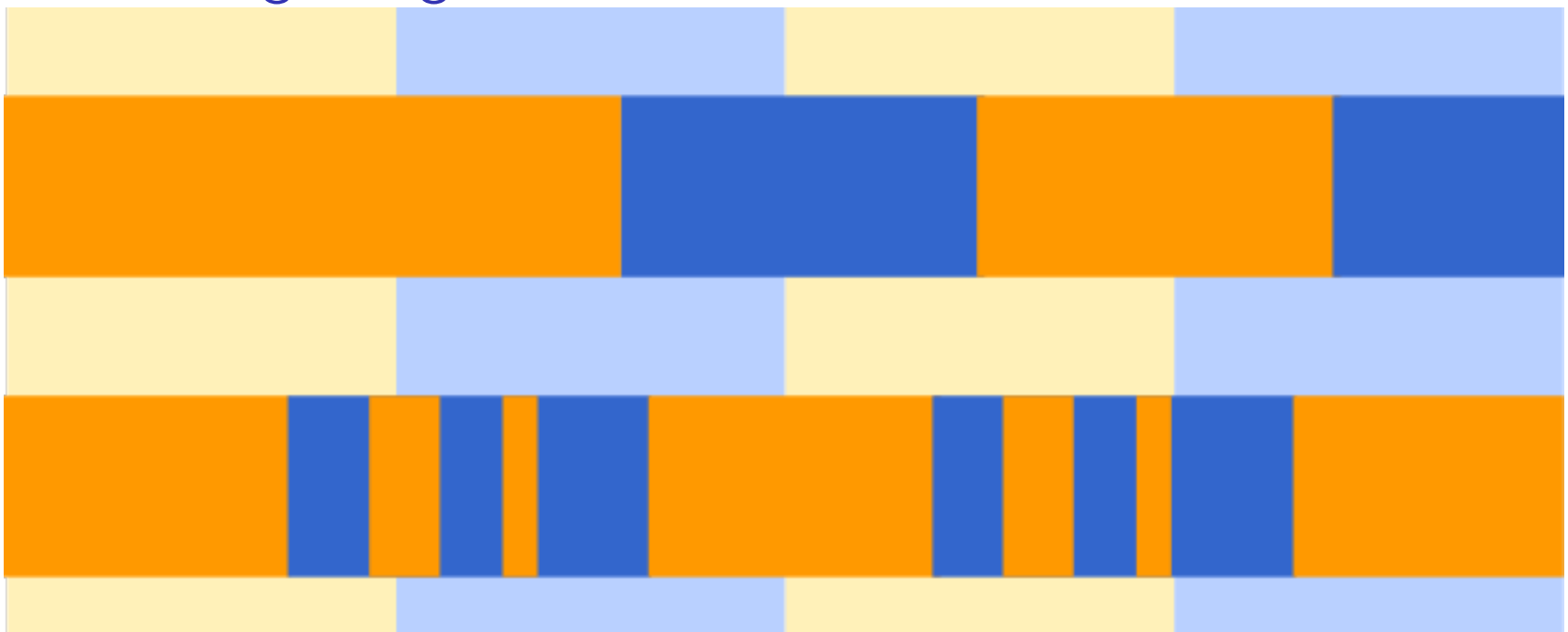


Biological experiments [Valrose]

Artificial lightning conditions

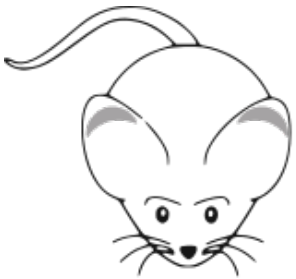
Biological experiments

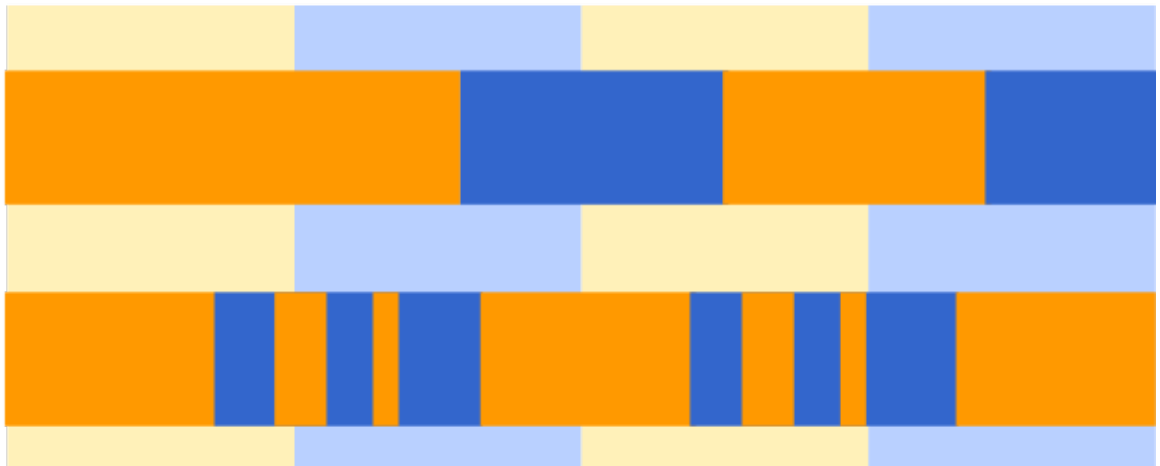
Artificial lightning conditions



Biological experiments

Gene knockout + artificial lightning conditions





Properties to address

- Address systems resilience (SR) model that incorporates costs of recovery
- Consider drastic changes in structure
- Circadian-clock: entrainment and coupling
- No information about distribution of delays

SR is formalized in Schwind N. et al., "Systems resilience: a challenge problem for dynamic constraint-based agent systems"

Design decision

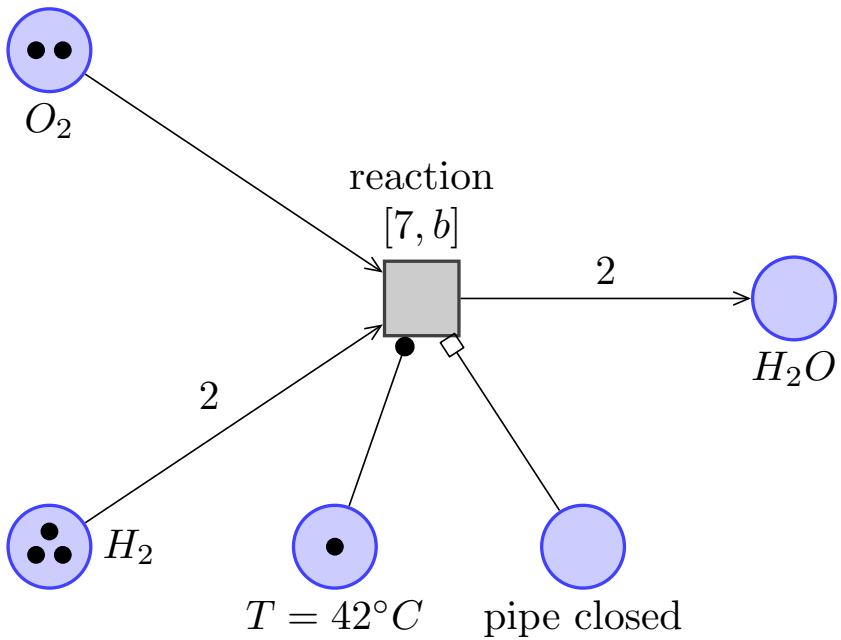
Analysis of chronometric properties

- Formalism: parametric time Petri Net
- Tool: Roméo [1]
- Variables: Boolean ("gene is expressed", "gene is not expressed")
- External stress: part of the model ("light is on", "light is off")

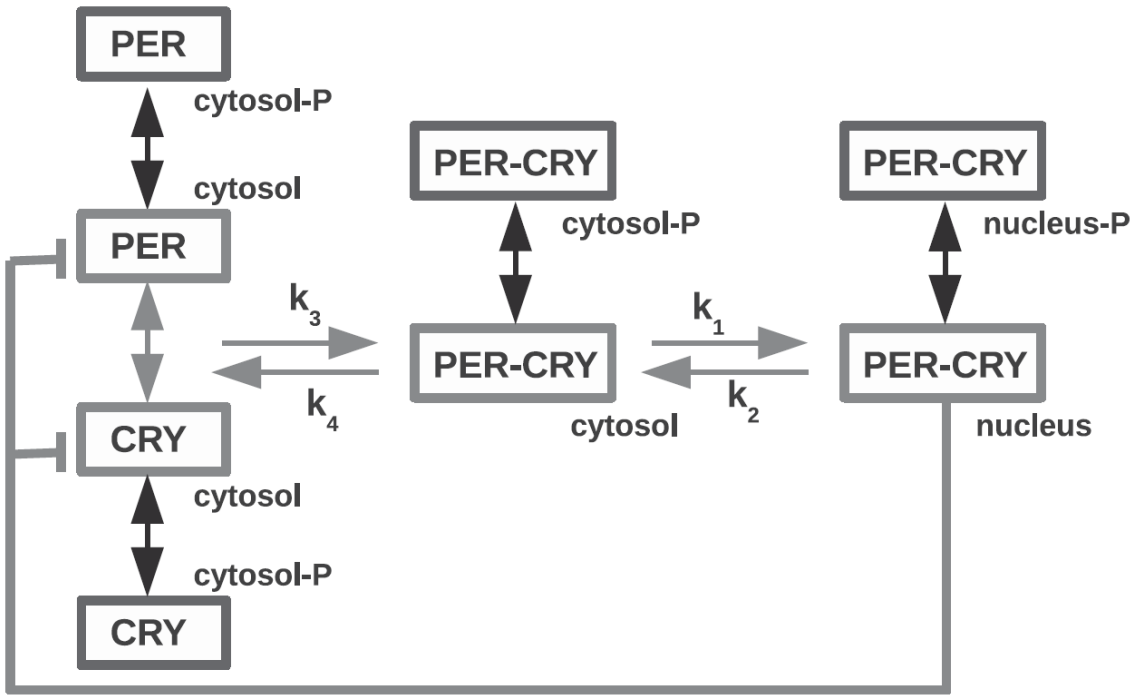
[1] Didier L. et al, "Romeo: A parametric model-checker for Petri nets with stopwatches"

Parametric time Petri Nets + extensions: H_2O example

Elements: places, transitions, arcs, read arcs ○, logical inhibitor arcs □, parametric interval firing function

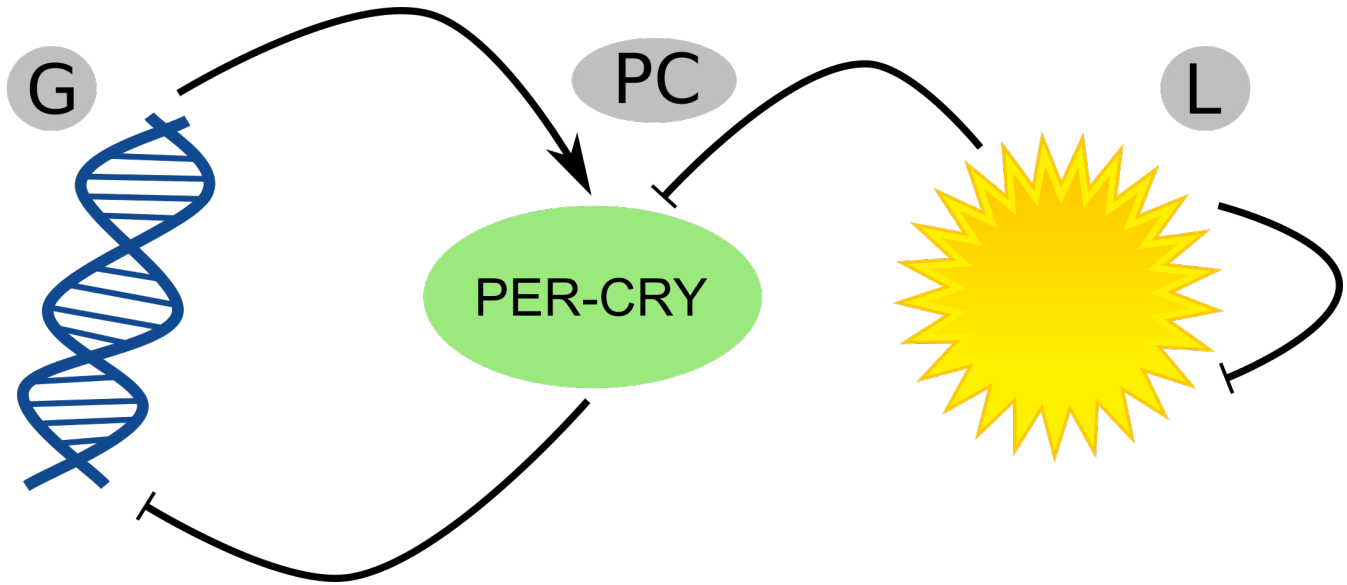


Circadian clock model



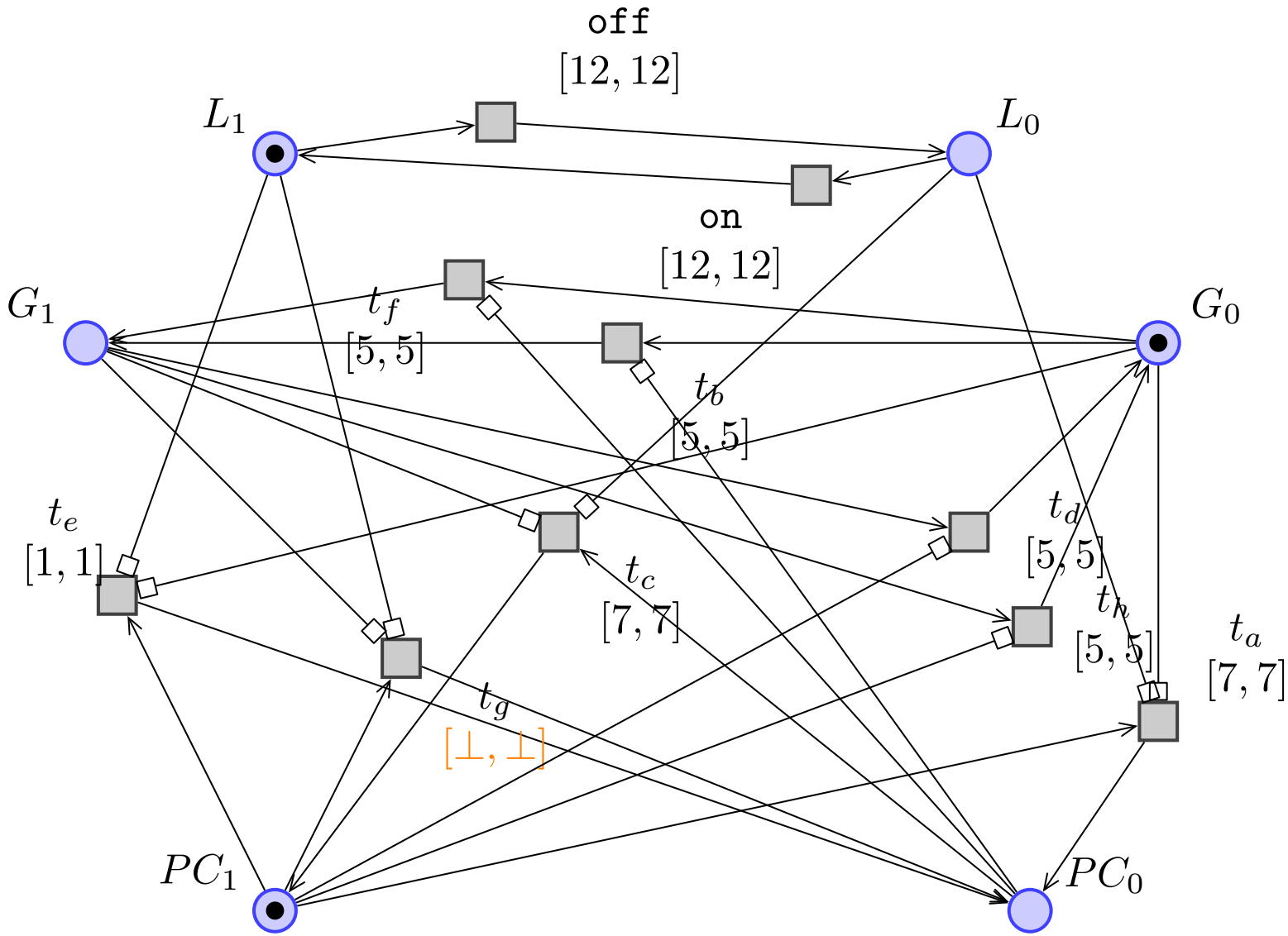
Model is taken from Comet, J-P. et al, "Simplified models for the mammalian circadian clock"

Simple circadian clock model



Model is taken from Comet, J-P. et al, "Simplified models for the mammalian circadian clock"

Petri net model of circadian clock



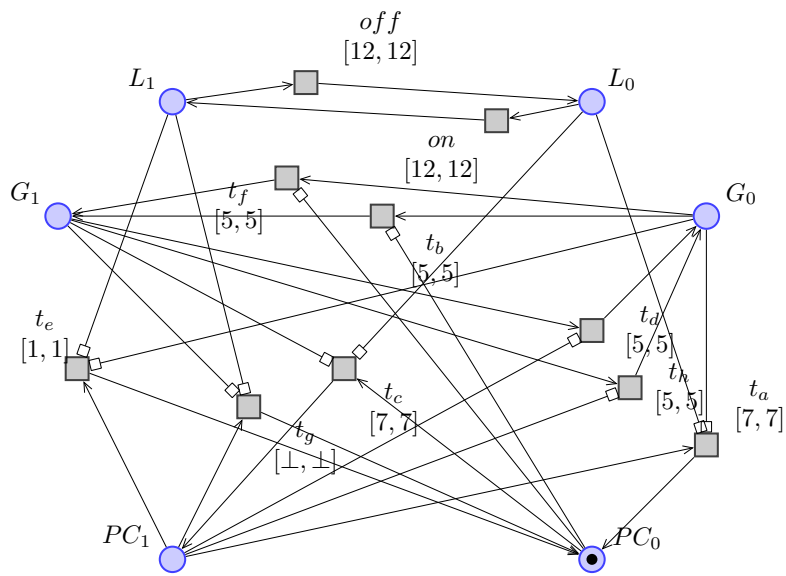
Model checking: PTPN-TCTL

- $\omega := E\varphi\ U_I\psi \mid A\varphi\ U_I\psi \mid EF_I\varphi \mid AF_I\varphi \mid EG_I\varphi \mid AG_I\varphi \mid \varphi \rightsquigarrow_{I_r} \psi$
- $GMEC ::= (\sum_{i=1}^{n} a_i * M(p_i)) \bowtie c \mid \varphi \vee \psi \mid \varphi \wedge \psi \mid \varphi \Rightarrow \psi$
- Can be extended with observers

Circadian clock properties

Permanent oscillation of PC

$$\phi = \Big(M(p_{PC0}) = 1 \rightsquigarrow_{[0,\tau_{0,1}]} M(p_{PC1}) = 1 \Big)$$
$$\wedge \Big(M(p_{PC1}) = 1 \rightsquigarrow_{[0,\tau_{1,0}]} M(p_{PC0}) = 1 \Big)$$

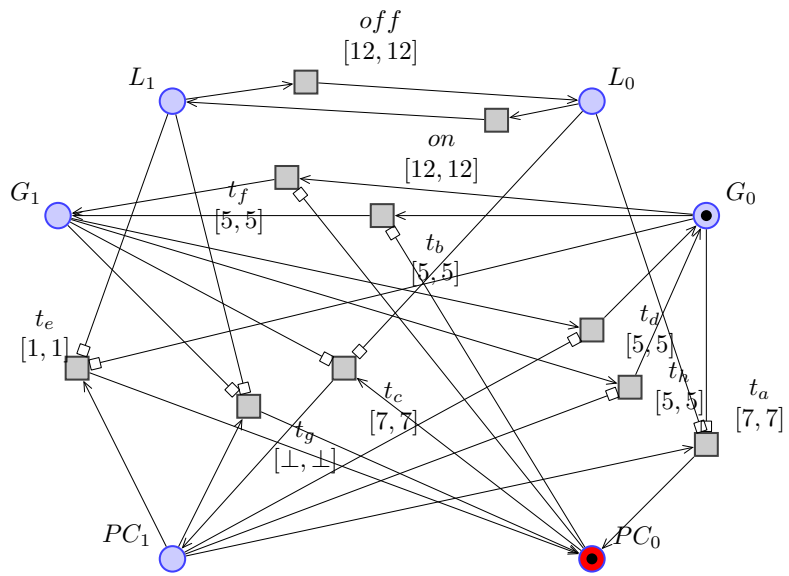


Properties inspired by Ballarini P., "Analysing biochemical oscillation through probabilistic model checking"

Circadian clock properties

Entrainment behavior: change of G

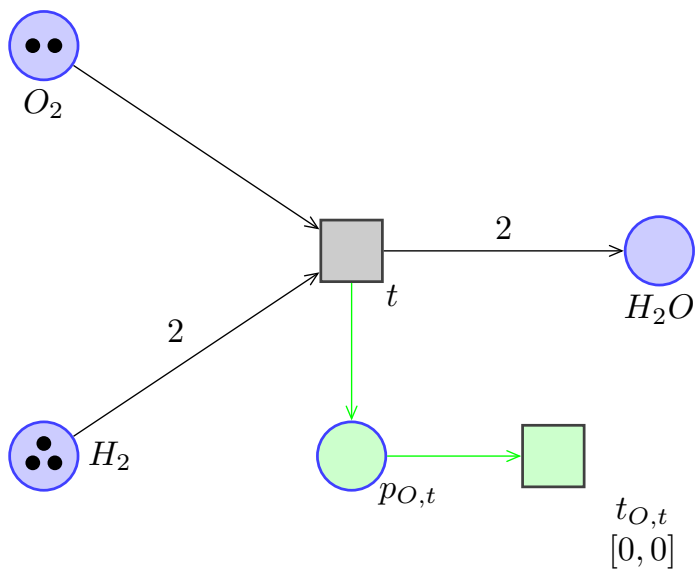
$$(M(p_{G0}) = 1 \wedge M(p_{PC0}) = 1) \rightsquigarrow_{[0,\tau_{0,1}]} (M(p_{G1}) = 1)$$



Properties with observers

Transitions redundancy

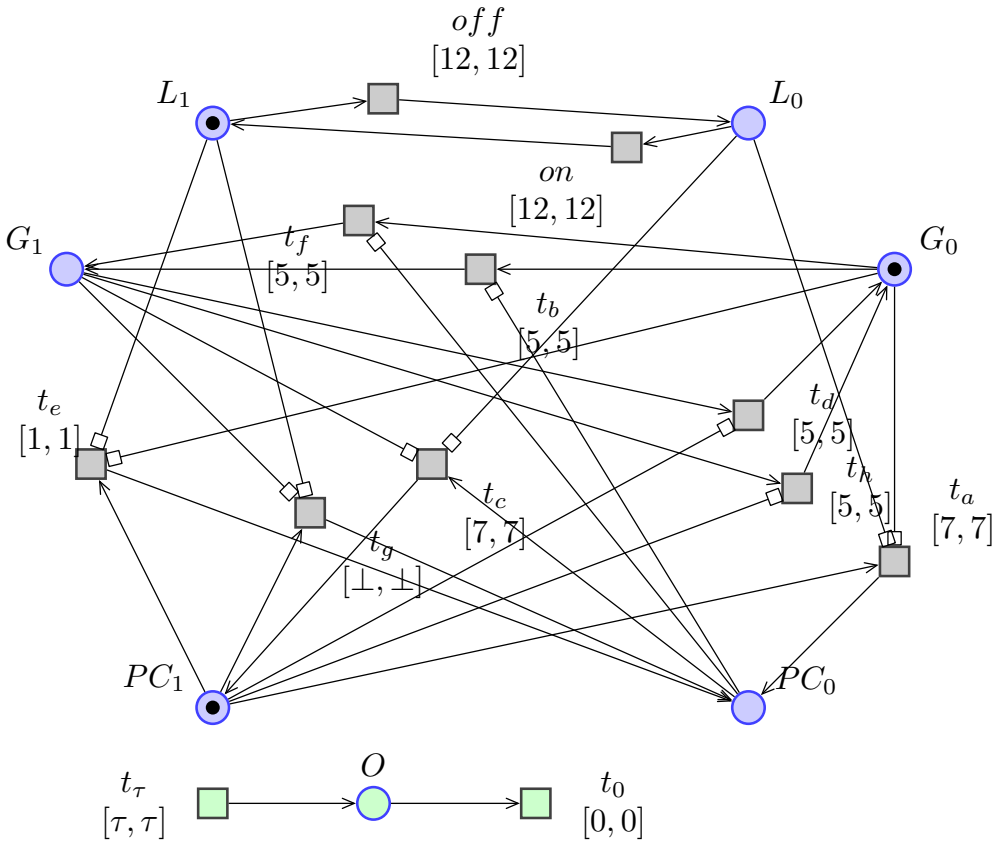
$$\bigwedge_{t \in \mathbf{T}} EF_{[0,\infty]} M(p_{O,t}) > 0$$



Properties with observers

Periodically τ observer behavior

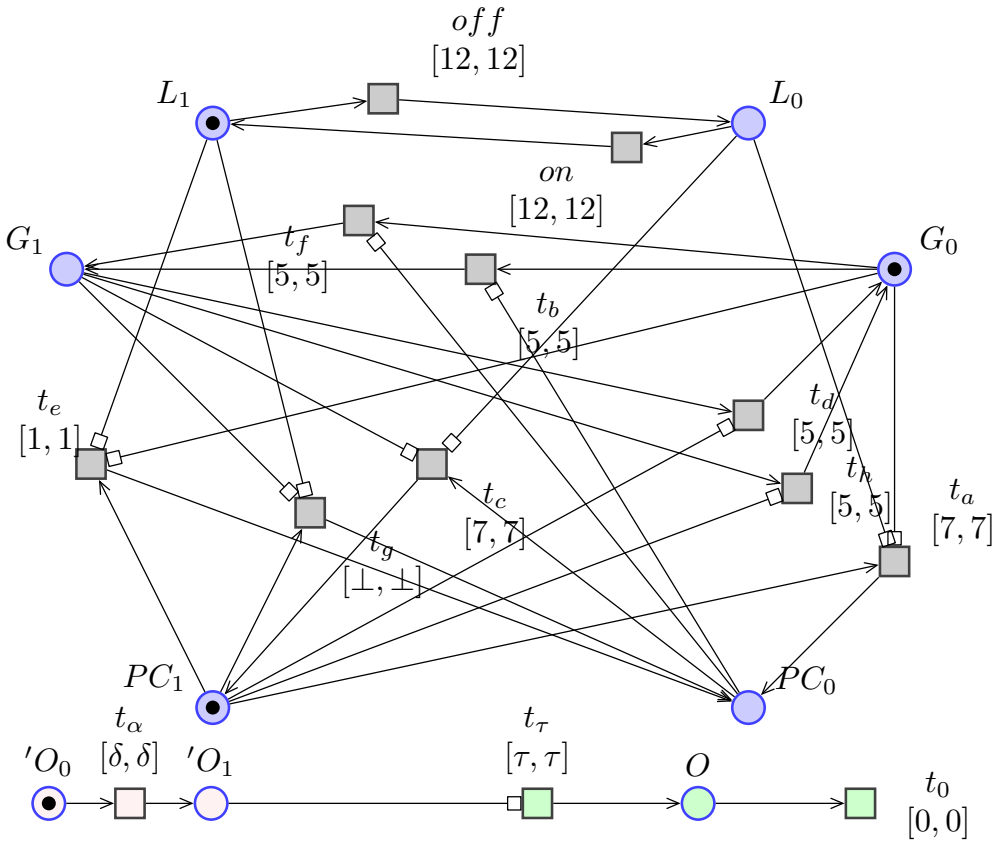
$$M(p_O) = 1 \rightsquigarrow_{[0,0]} [M(p_{L1}) = 1 \wedge M(p_{G0}) = 1 \wedge M(p_{PC1}) = 1]$$



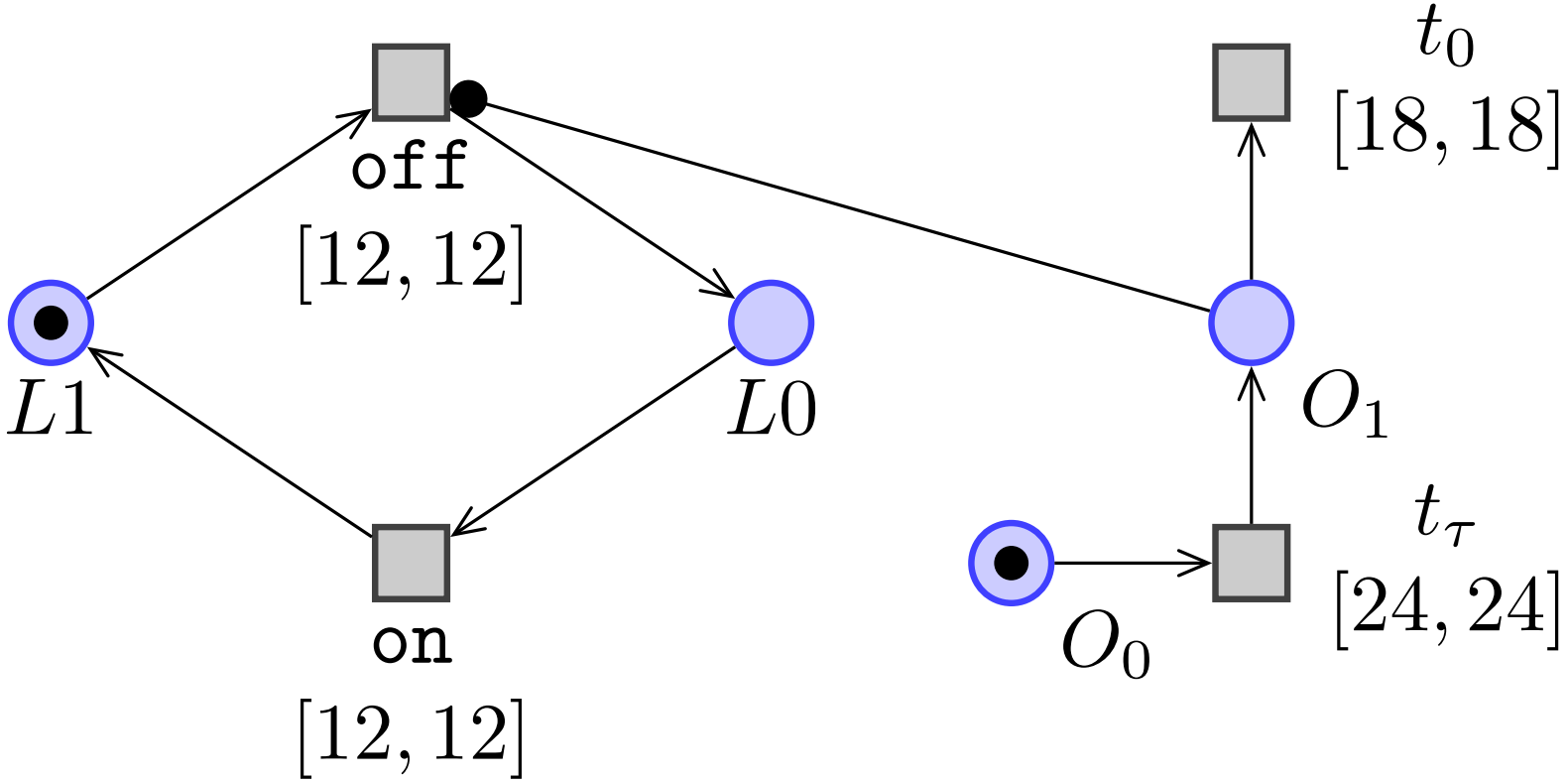
Properties with observers

Periodically τ observer behavior with initial delay δ

$$M(p_O) = 1 \rightsquigarrow_{[0,0]} [M(p_{L1}) = 1 \wedge M(p_{G0}) = 1 \wedge M(p_{PC1}) = 1]$$



Jet-lag effect



Contribution

- Transformation MVN $+$ time info $\mapsto$ PTPN
- Proof of concept: several resilience-related properties introduced for biological systems
- Methodology to create such properties ($+$ using observers)
- Model checking of simple circadian clock model

Open questions and problems

- PTPN-TCTL: no nesting
- PTPN-TCTL: only local-time properties
- Intervals: use $[a, b]$ instead of simple $[a, a]$
- Time: delays in minutes
- Resilience [Japan]: establish the cost function (complexity of 'recovery' in PTPN model)
- Resilience [Japan]: establish the connection to SR model
- Nominal behaviour after the adaptation

Future work

- Markovian and non-Markovian stochastic approaches
- Advanced model of circadian clock (available)
- Analysis of experimental data (available)

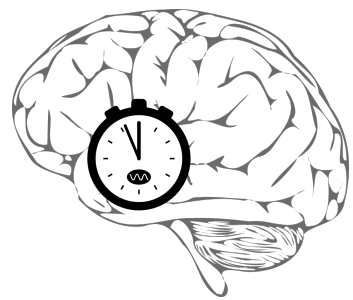
CMSB2015 inspired

- Usage of hybrid I/O automata and counting MTL (@ Marta Kwiatkowska)
- Process Hitting framework to easier treat multiple levels species and define recovery cost (@ Emna Ben Abdallah, Maxime Folschette, Morgan Magnin)
- Minimal model to satisfy properties and provide oscillations (@ Wassim Abou-Jaoude)

Acknowledgements

- MOU between NII and CS Graduate School of Saarland University
- French ANR Hyclock
- JSPS

Questions?



Coupling of oscillators

The current approach is capable to treat coupled oscillators if

- all parts of the system are represented in the same PTPN formalism
- reasonable upper bounds for parametric clocks are given a-priori

Resilience

The name for the group of properties

- Resistance
- Recoverability
- Functionality
- Stability

In addition to the reaction to changes in the environment the resilience addresses changes in structure of the system itself.

[1] Definition is formalized in Nicolas Schwind et al., "Systems resilience: a challenge problem for dynamic constraint-based agent systems"

Scalability of the approach

Roméo tool is aimed at conducting model-checking for Time Petri Nets such that

- parametric state space computation is based on State Classes
- verification of parametric properties on reachable markings is conducted on-the-fly

The following issues can restrict the scalability of the approach

- parametric clocks for which the upper bound is not known
- number of parametric clocks