Model-based Investigation of the Effect of the Cell Cycle on the Circadian Clock through Transcription Inhibition during Mitosis

CMSB 2015 – September 18th

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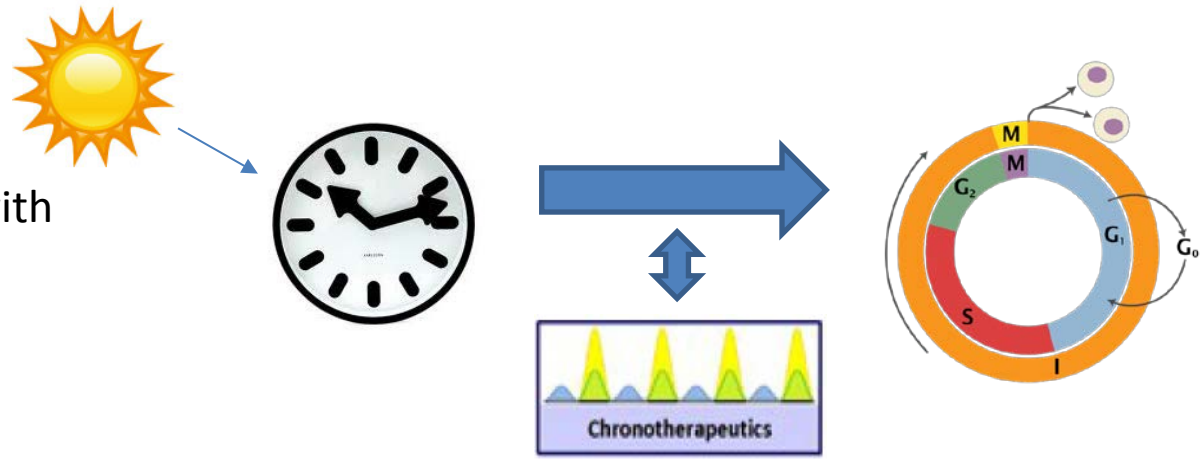
Lifeware, Inria Paris Rocquencourt

The cell cycle and the circadian clock



Context:

Optimizing cancer treatment with chronotherapy

Two complex systems:

Circadian Clock: autonomous cellular oscillator with a 24h period, synchronised by the central clock
Cell Cycle: divisions every 24h

Question:

What are the interactions between the two?

Classical view:

Entrainment in period and phase of the cell cycle by the circadian clock (Matsuo et al 2003)
Gating by Wee1

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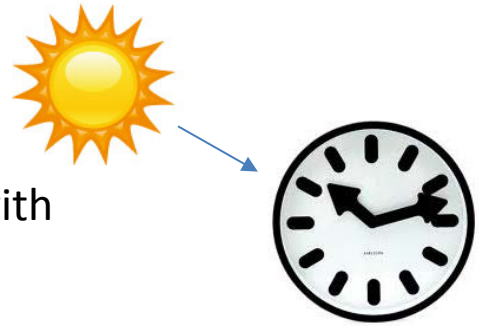

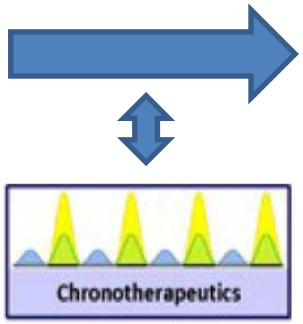

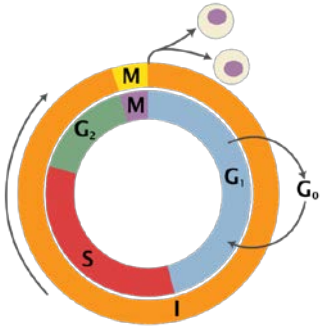

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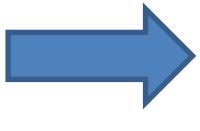
[Lodish et al. 03]

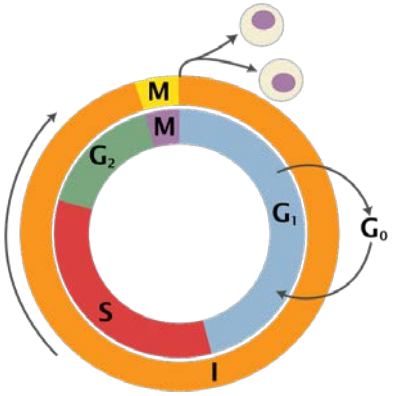
Paradox: experimental data show an acceleration of the circadian clock at high FBS

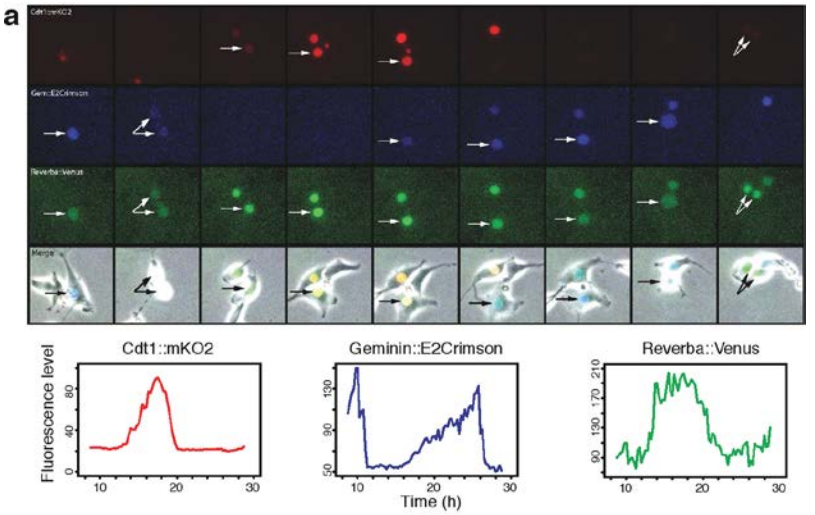
Experiments and observations

- Fluorescent markers of the cell cycle and the circadian clock
- Time series in individual mice fibroblasts
- Medium with various concentrations of serum (FBS) to modulate cell cycle length
  - → **Acceleration** of the circadian clock in fastly dividing cells **– and not in confluent cells**
- Some experiments begin with a Dexamethasone pulse
  - → Various modes of phase-locking

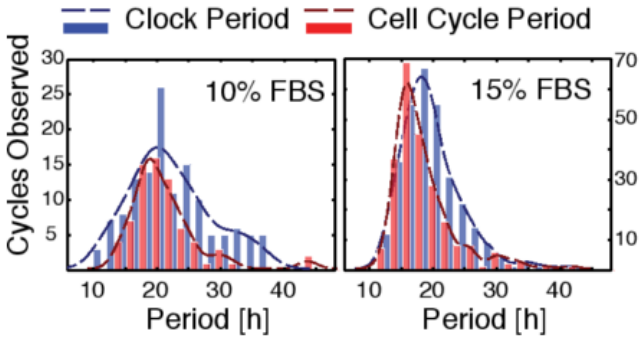
These experiments suggest that in some conditions there is **a control of the circadian clock by the cell cycle**







24h → 17h



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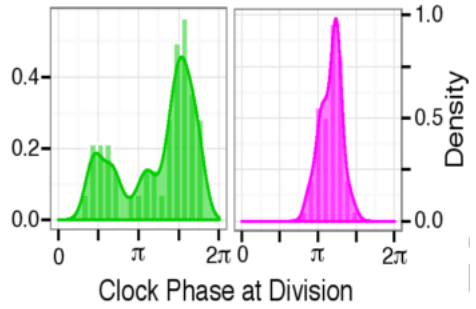

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[Feillet-Krusche-Tamanini 2014]

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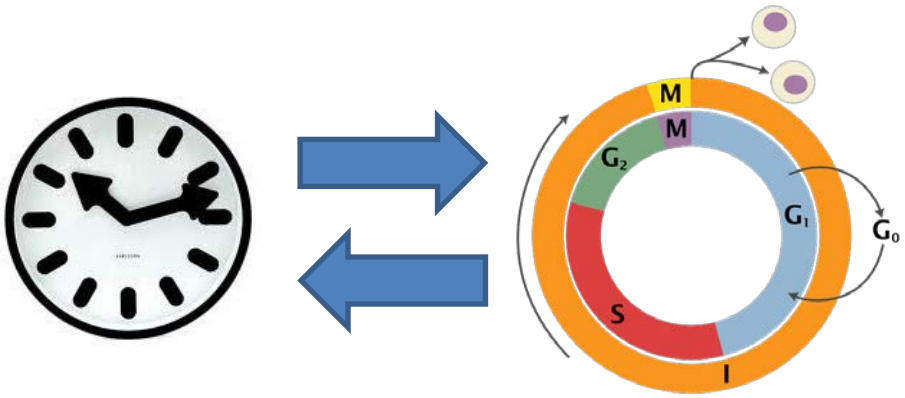

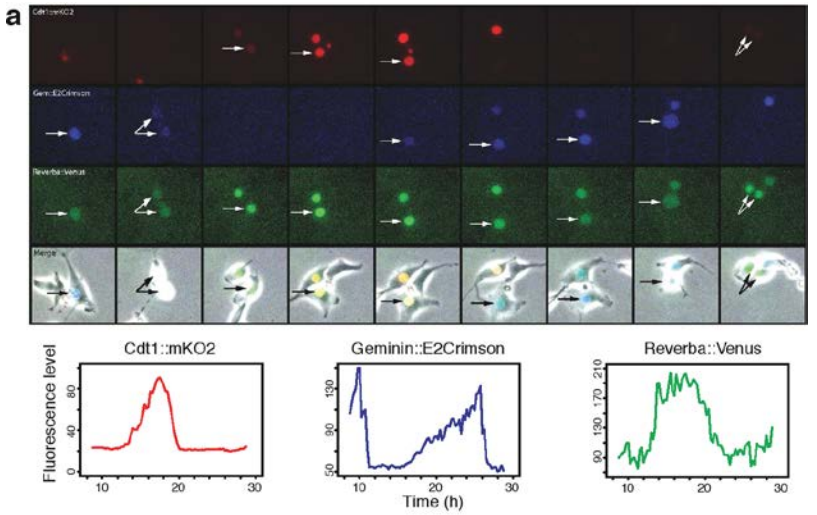

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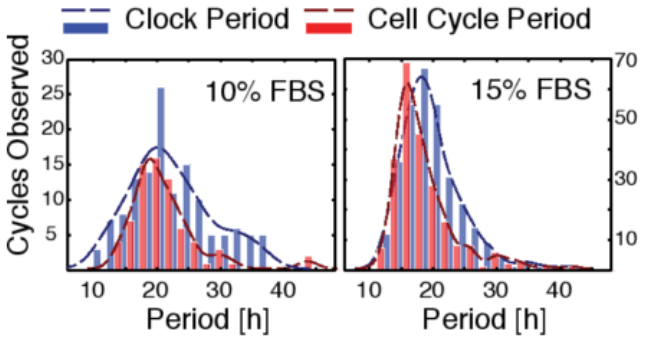

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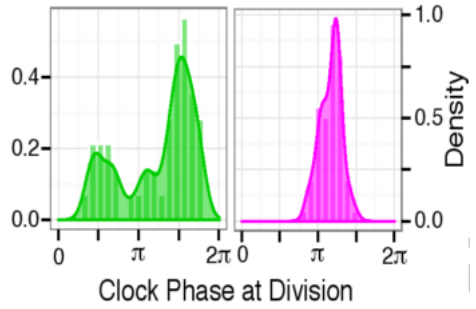

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[Feillet-Krusche-Tamanini 2014]

Explaining hypothesis: inhibition of the transcription during mitosis

Model-based investigation of that **reverse coupling** from the cell cycle to the circadian clock

- Reusing already existing **differential models from the literature**:
  Cell cycle: Qu et al 2003
  Circadian clock: Relogio et al 2011

- Coupling by inhibition of transcription during mitosis

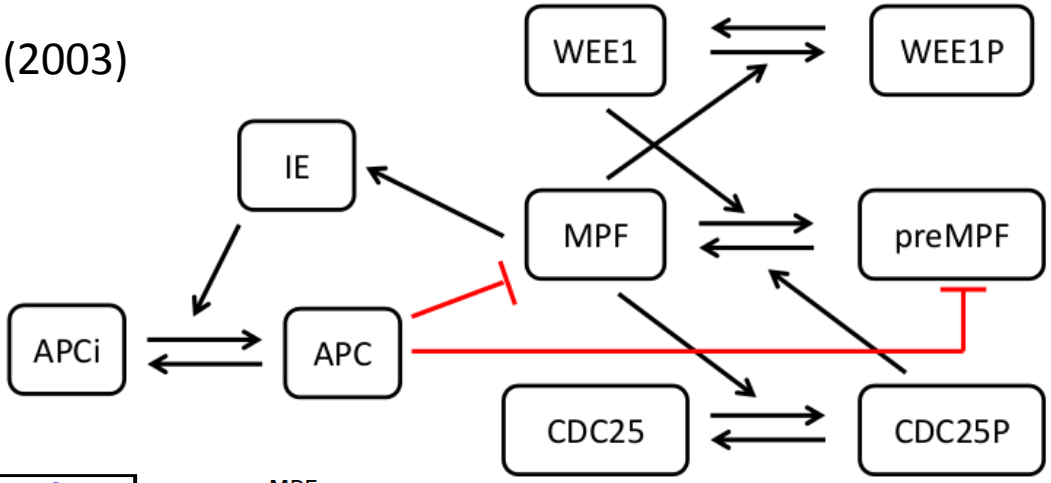
$$S * \frac{J^n}{J^n + ([MPF]/[preMPF])^n}$$

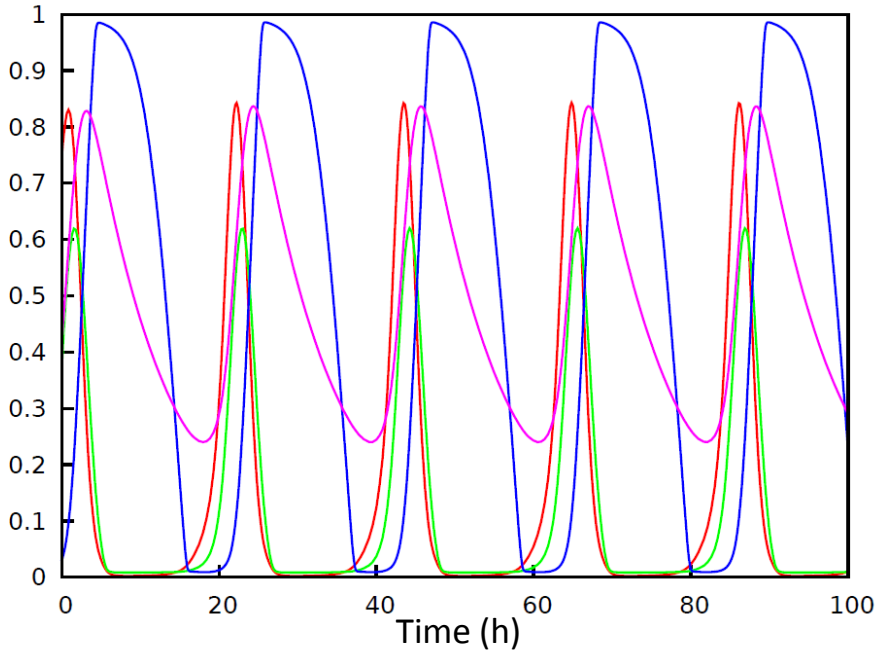
- **Model analysis** assisted with formal methods [CMSB2014]
  Parameter inference

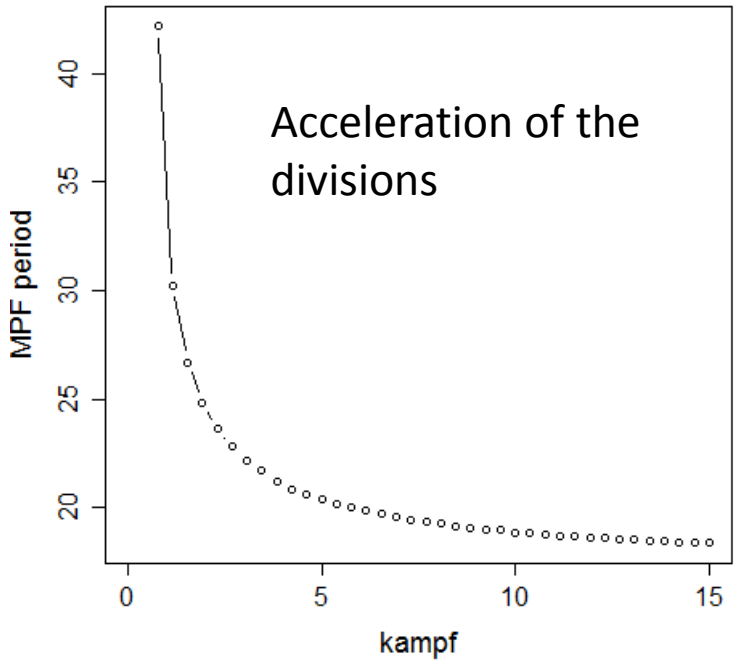
- **Predictions**: mechanisms and perturbations, treatment optimization

Modeling the control of the circadian clock by the cell cycle

- Cell cycle : Qu, McLellan, Weiss (2003)
  - Mitosis phase
  - 10 equations, 31 parameters



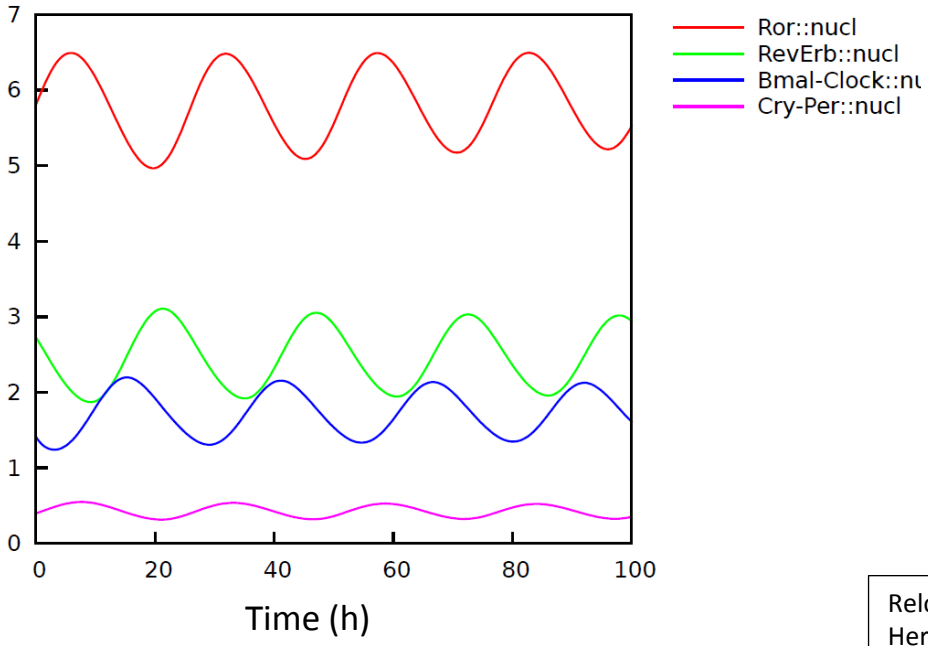




Qu, Z., MacLellan, W. R., & Weiss, J. N. (2003). Dynamics of the cell cycle: checkpoints, sizers, and timers. Biophysical Journal.

Modeling the control of the circadian clock by the cell cycle

- Circadian clock : Relogio Herzel (2011)
  - 20 species, 71 parameters
  - **The values of 60 parameters were determined to fit experimental data (amplitude and phase) in liver cells**
  - 5 genes : Per, Cry, Reverb, Ror, Bmal.
  - 2 negative feedback loops
  - 2 positive feedback loops



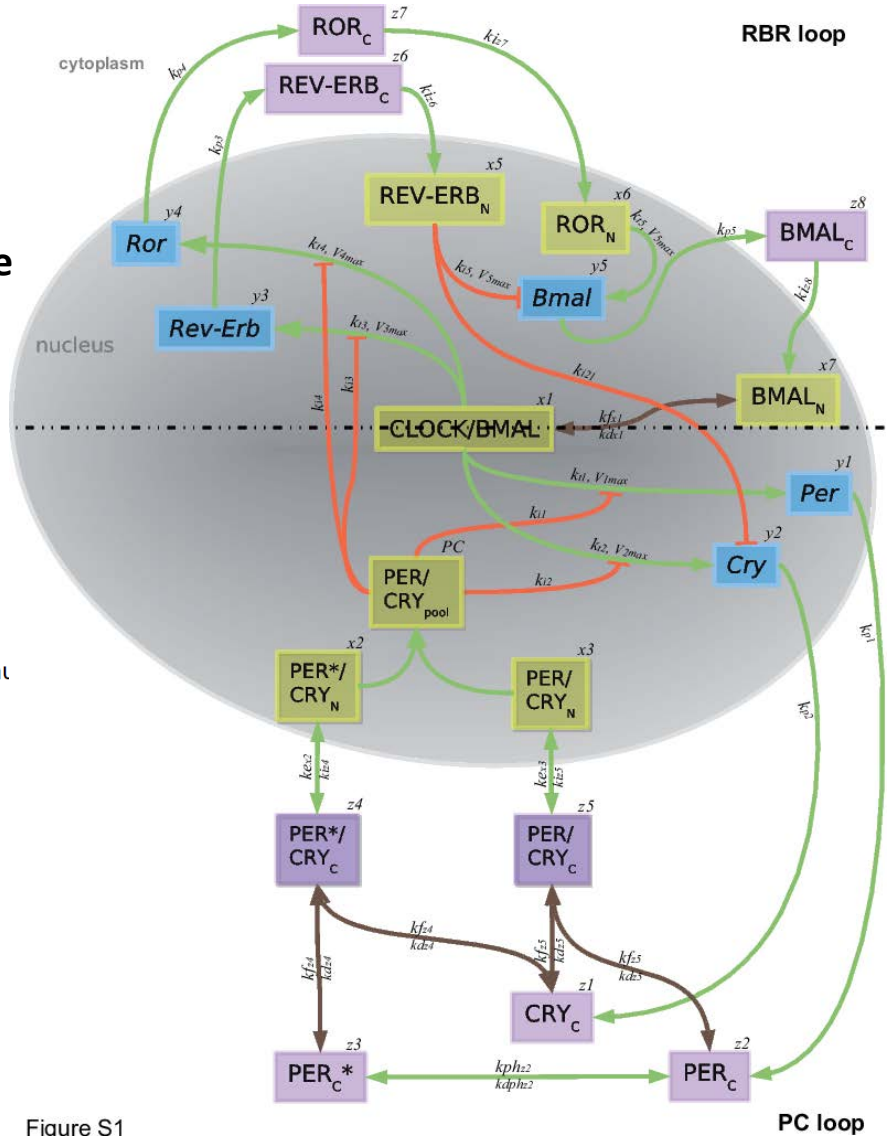
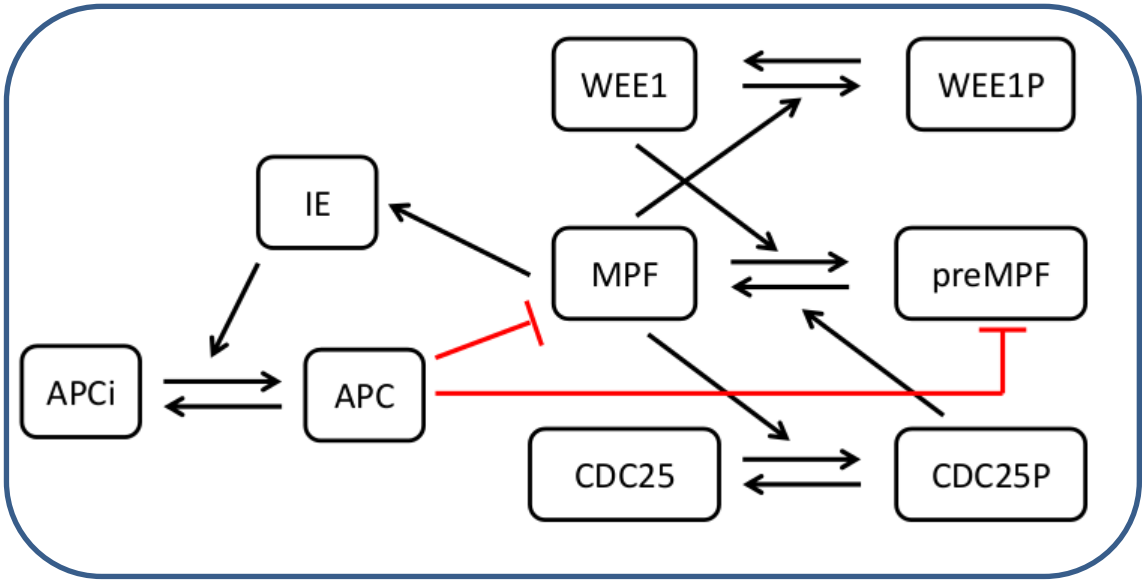


Figure S1

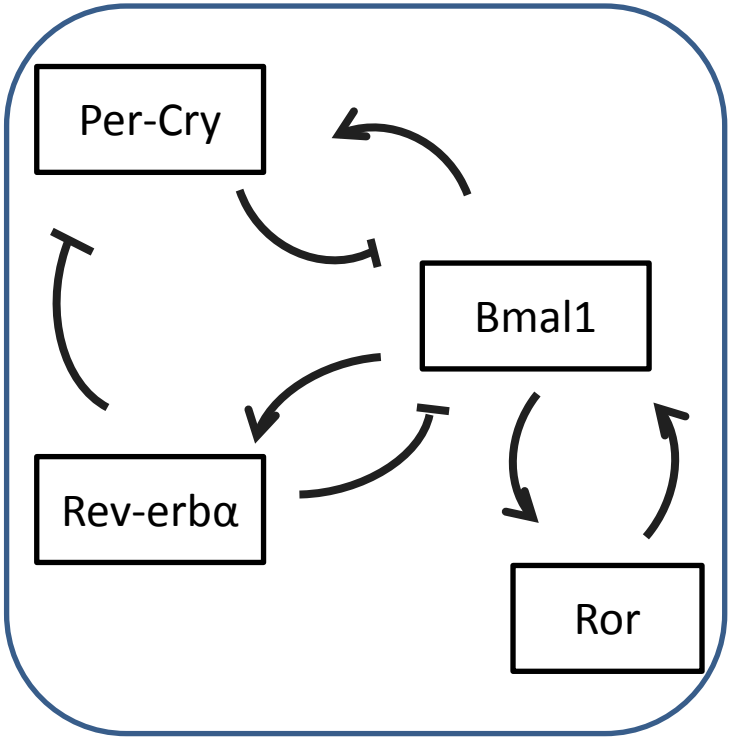
Relógio, A., Westermark, P. O., Wallach, T., Schellenberg, K., Kramer, A., & Herzel, H. (2011). Tuning the mammalian circadian clock: robust synergy of two loops. PLoS Computational Biology.

Modeling the control of the circadian clock by the cell cycle



Cell Cycle

Circadian Clock

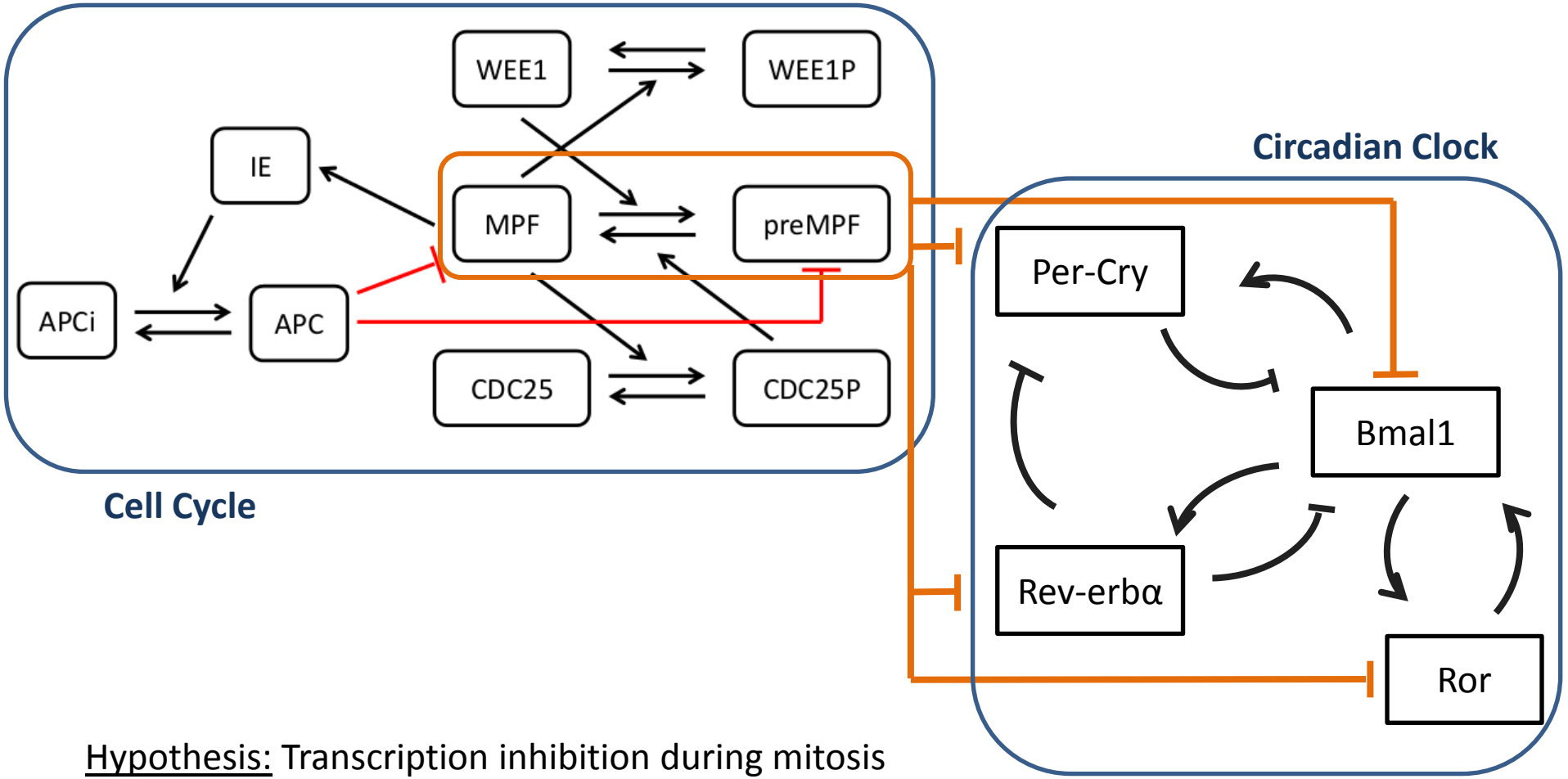


Hypothesis: Transcription inhibition during mitosis

$$S * \frac{J^n}{J^n + ([MPF]/[preMPF])^n}$$

for each synthesis expression S in the clock

Modeling the control of the circadian clock by the cell cycle



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Formalizing the dynamical behaviors with temporal logic QFLTL(R)

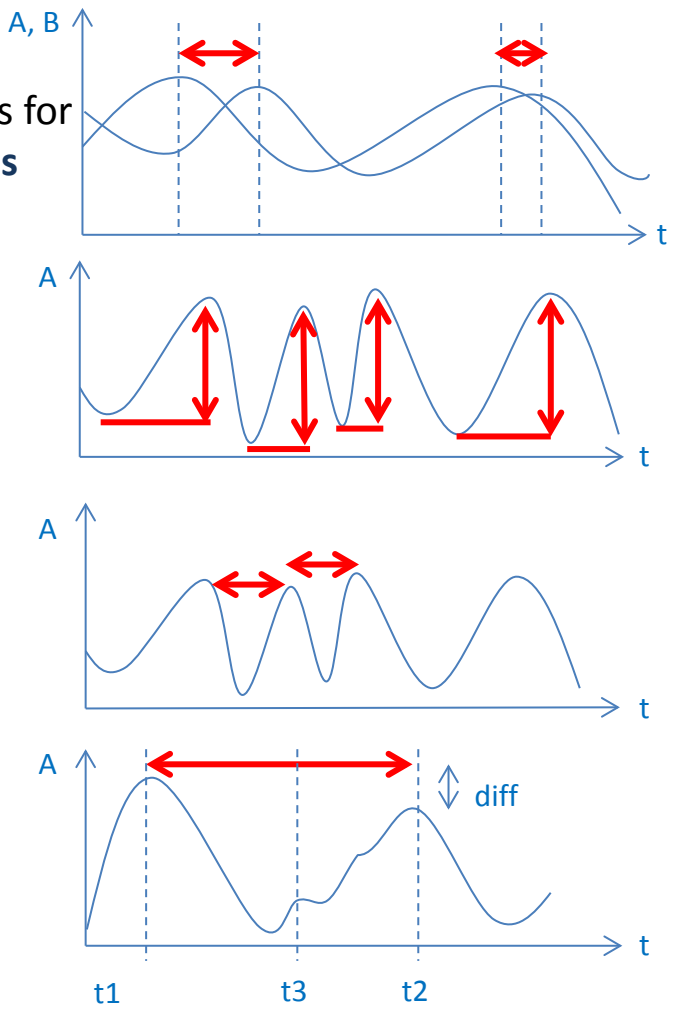
- **QFLTL:** expressing qualitative or quantitative dynamical behaviors for oscillatory systems such as **period, amplitude, phase, oscillations regularity**

- **Applications:**
  - **Data analysis, Model checking, Model analysis, Parameter inference (calibration)**
  - Tools implemented in **BIOCHAM**

- **Built-in functions:**

  Ex: **amplitude**(Mol,amp), **period**(Mol,per),

  phase(Mol1,Mol2,phase)



Temporal specification: regular oscillations with a fixed period

```
period([RevErb::nucl],[period])
& Exists([maxdiff1,maxdiff2,maxpeak],
        maxDiffDistancePeaks([RevErb::nucl],[maxdiff1])
        & maxDiffAmplPeaks([RevErb::nucl],[maxdiff2])
        & maxAmplPeaks([RevErb::nucl],[maxpeak]])
        & 4*maxdiff1 < period + errordiff1
        & 10*maxdiff2 < maxpeak + errordiff2
        & maxpeak > 0.1 + errorampl)
```

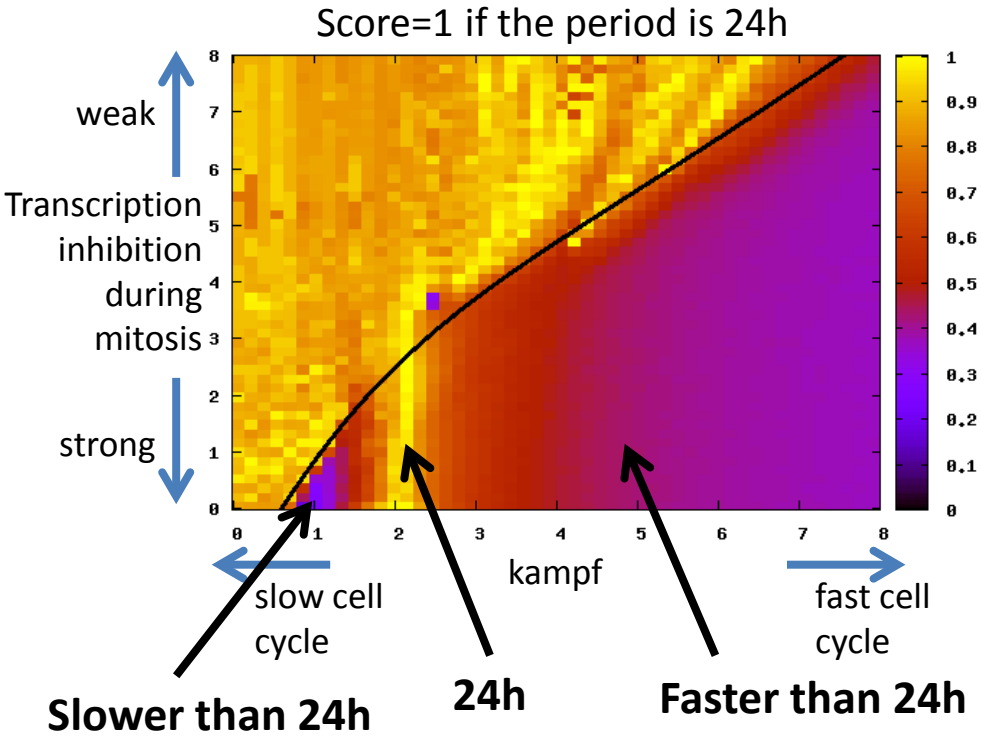
http://lifeware.inria.fr/biocham

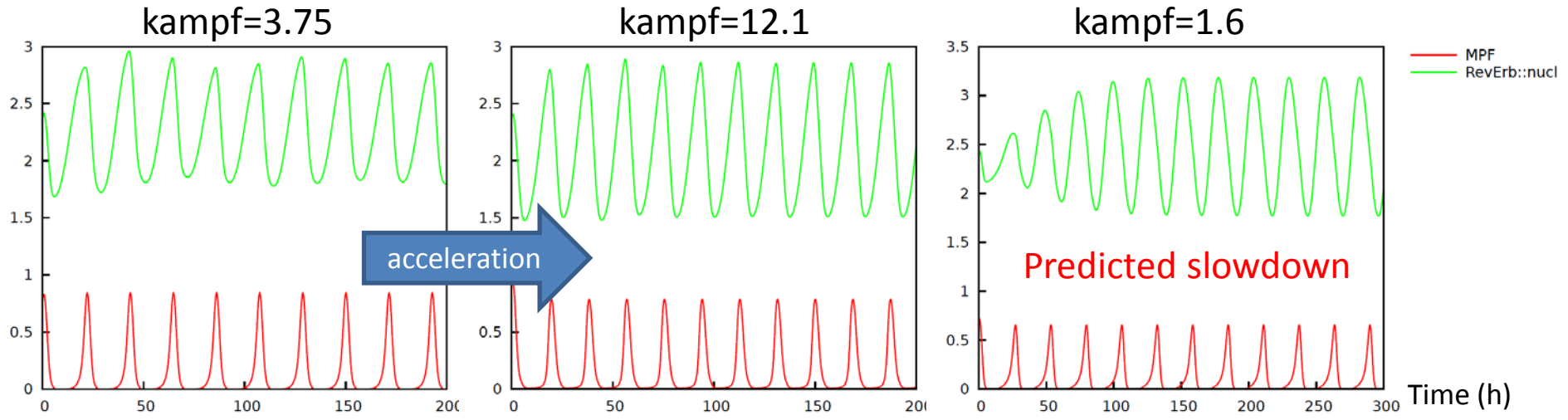
Results without Dexamethasone

Landscape of the score for an objective period of 24h for the circadian clock:

Domain of entrainment of the clock period by the cell cycle

Kampf	FBS (%)	Circadian clock period (h)	Cell division period (h)
3.75	10	21.43	21.30
12.1	15	18.60	18.60
1.6	5 ?	26.16	26.32





Results with Dexamethasone

Dexamethasone pulses induce the expression of *per1*

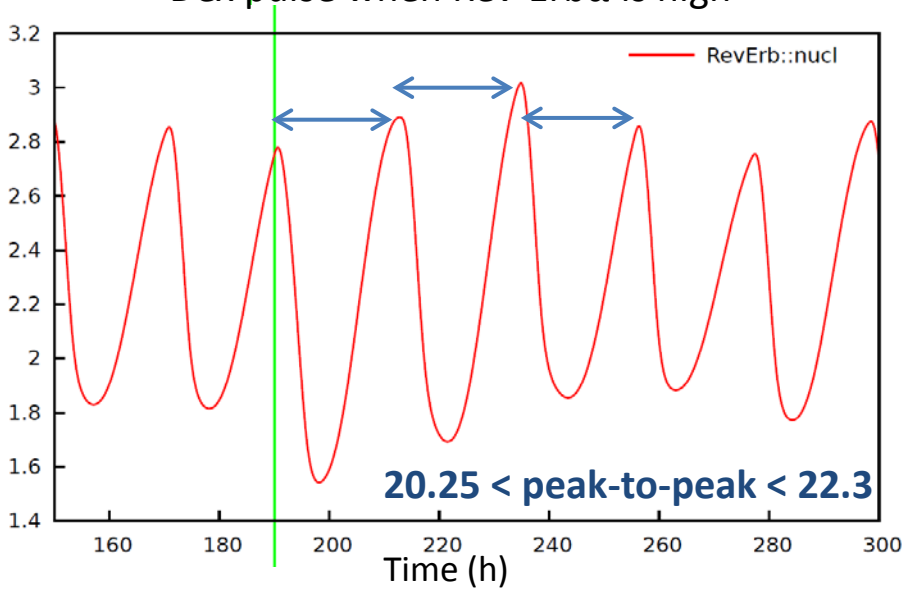
→ extension of the model with a **2h event** increasing the synthesis of mPER

→ **The clock is disrupted** and then returns to the observed entrainment, regardless of the medium but **depending on the time of the pulse**

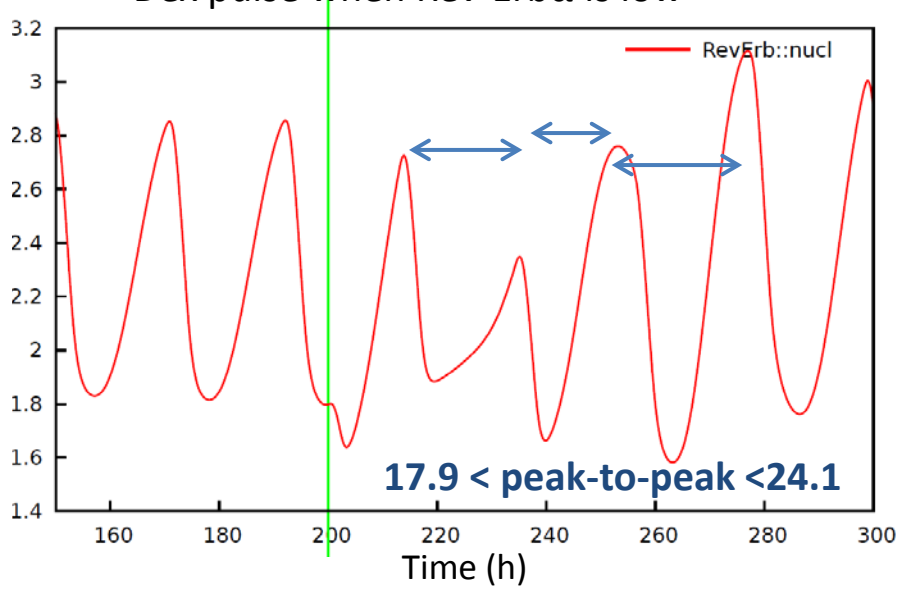
→ **Transitory variations** could explain the noisy data

Med	No dexamethasone		Dexamethasone	
	Clock period	Division period	Clock period	Division period
FBS 10	21.9h ± 1.1h	21.3h ± 1.3h	24.2h ± 0.5h	20.1h ± 0.94h
FBS 15	19.4h ± 0.5h	18.6h ± 0.6h	NA	NA
FBS 20	NA	NA	21.25h	19.5h
FBS 20	NA	NA	29h	16h

Dex pulse when Rev-Erbα is high



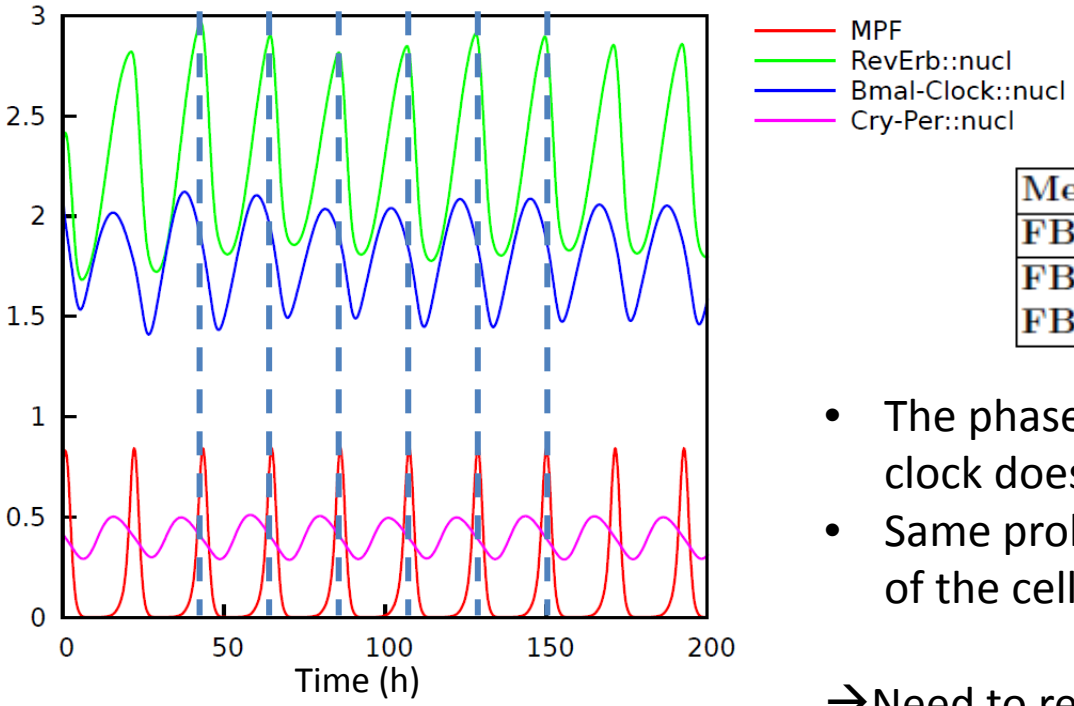
Dex pulse when Rev-Erbα is low



Conclusion 1

- Explanation hypothesis for the control of the circadian clock: **inhibition of the transcription during mitosis**
- The hypothesis reproduces the **acceleration of the circadian clock** by a fast cell cycle
- **Prediction** of the model: **entrainment in period of the circadian clock** even in slowly dividing cells

Discrepancies on the phases



Phase between MPF and Rev-Erbα

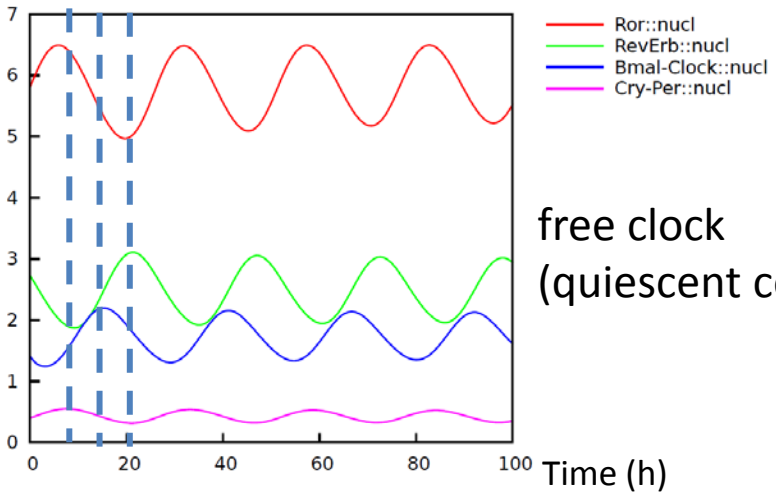
Medium	Experimental data	Model simulation
FBS 5	NA	18.6h
FBS 10	3.82h	20.7h
FBS 15	3.98	17.8h

- The phase between the mitosis and the circadian clock does not match the data
- Same problem in published models for the control of the cell cycle by the circadian clock

→Need to revise the model of the circadian clock?
→Consider other coupling hypothesis?

Prediction of the model

In quickly dividing cells, the phase shifts between the different components of the clock are shorter than in quiescent cells



free clock (quiescent cells)

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Conclusion 2

- Remaining discrepancies on the **circadian phase at division**
- **Prediction** of the model: shorter phase shifts between the components of the clock

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Acknowledgements

- **Lifeware Team**

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ANR HyClock
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Céline Feillet

- **GENCI cluster**

Public high performance computing resources