Systems biology of coupled biological oscillators

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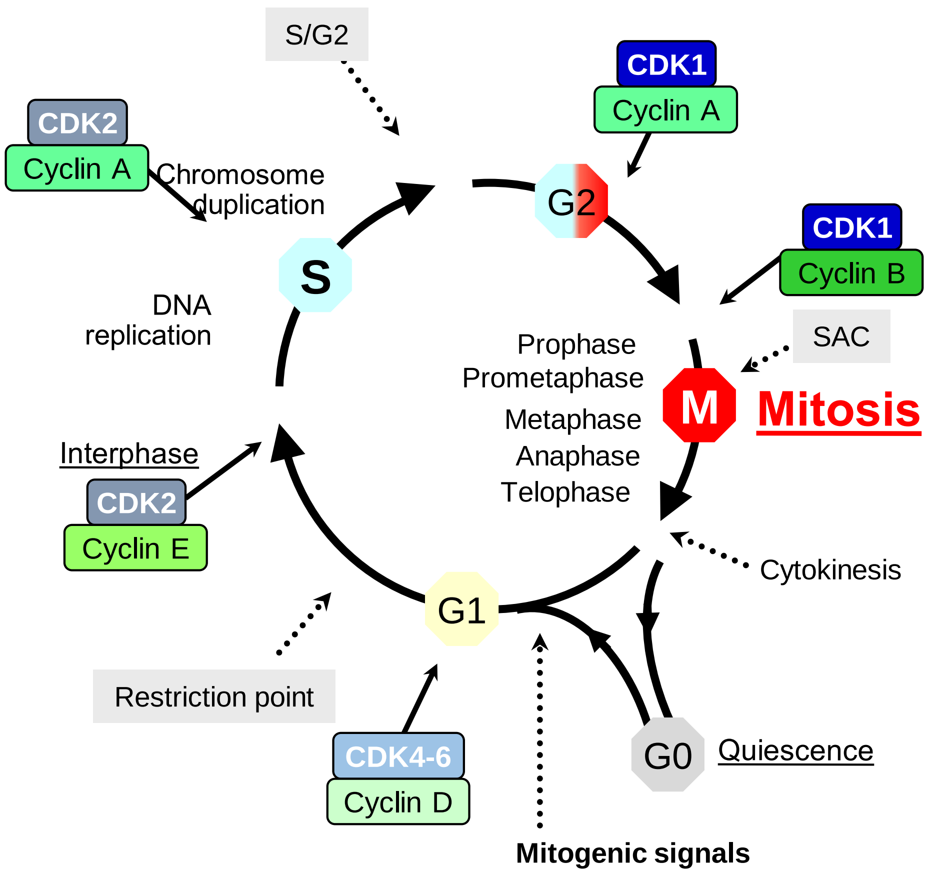
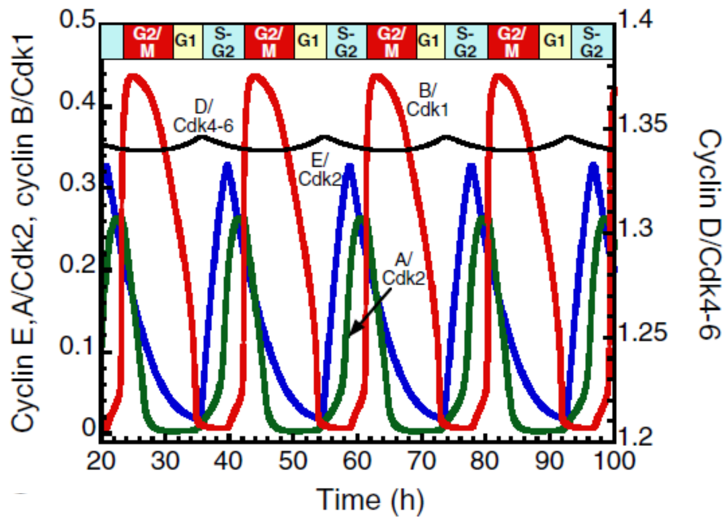
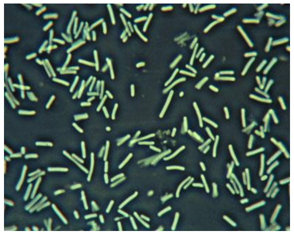
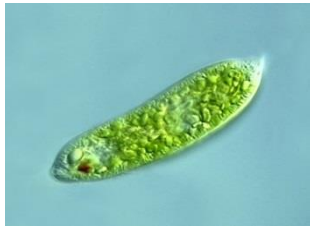
The CDK oscillator drives the cell cycle





Gérard & Goldbeter, PNAS 2009

Daily rhythms of cell division cycle are universal

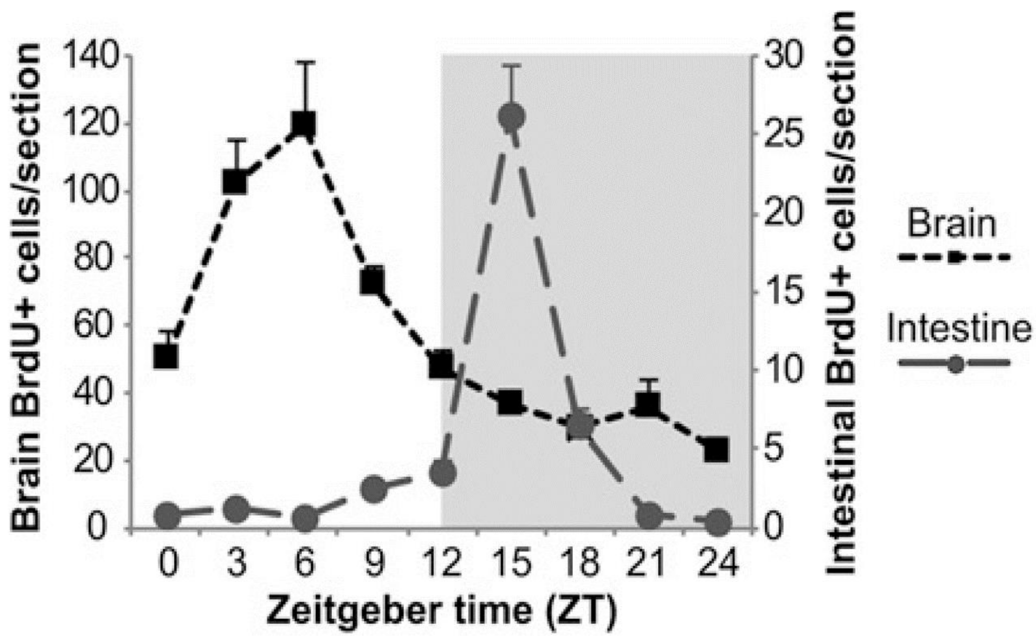




- *Kellicott, W. The daily periodicity of cell division and of elongation in the root of Allium.* ***Bull. Torrey Bot. Club****, 31:* ***1904***

- *Fortuyn-Van Leyden, Droogleever. Some observations on periodic nuclear division in the cat.* ***Proc. Soc. of Sciences****, Amsterdam, 19: 38,* ***1916.***

- *Thuringer, J. M. Studies on cell division in the human epidermis.* ***Anat. Record****, 40: 1,* ***1928***

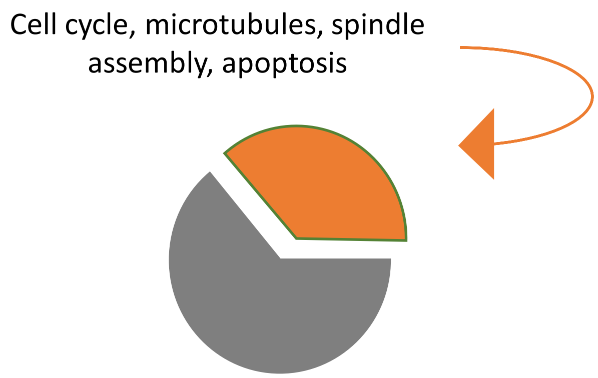
DNA synthesis in zebrafish tissues



Laranjeiro et al, PNAS 2012

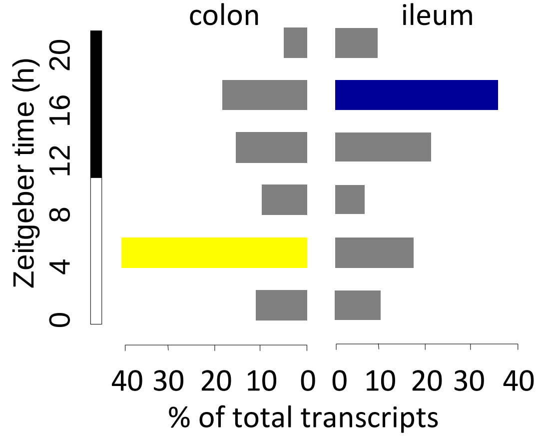
Cell cycle transcripts are enriched in the colon mucosa circadian transcriptome

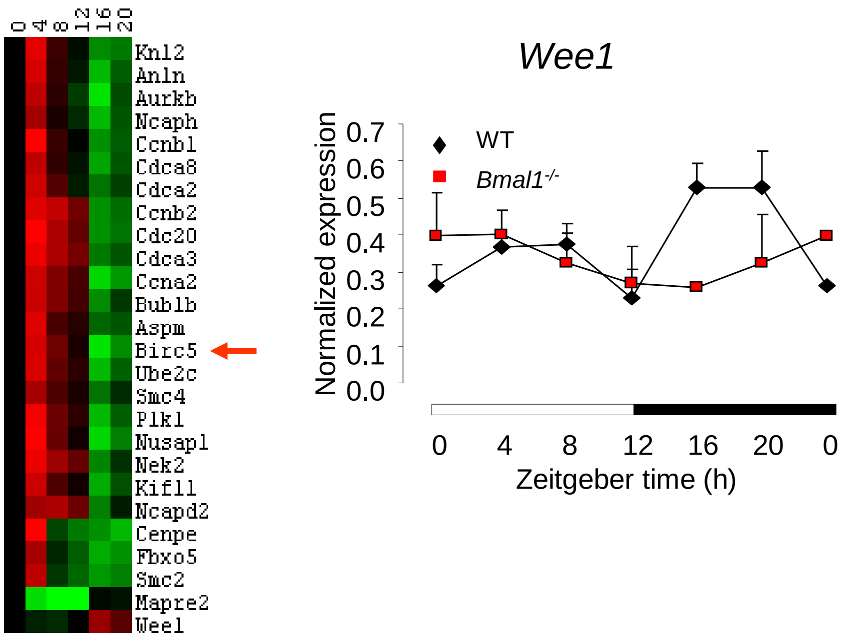
Circadian transcriptomics



Colon mucosa

GO term	Count	%	p-value
GO:0022402~cell cycle process	36	22	1.91E-24
GO:0000279~M phase	32	20	2.38E-24
GO:0007049~cell cycle	42	26	5.55E-24

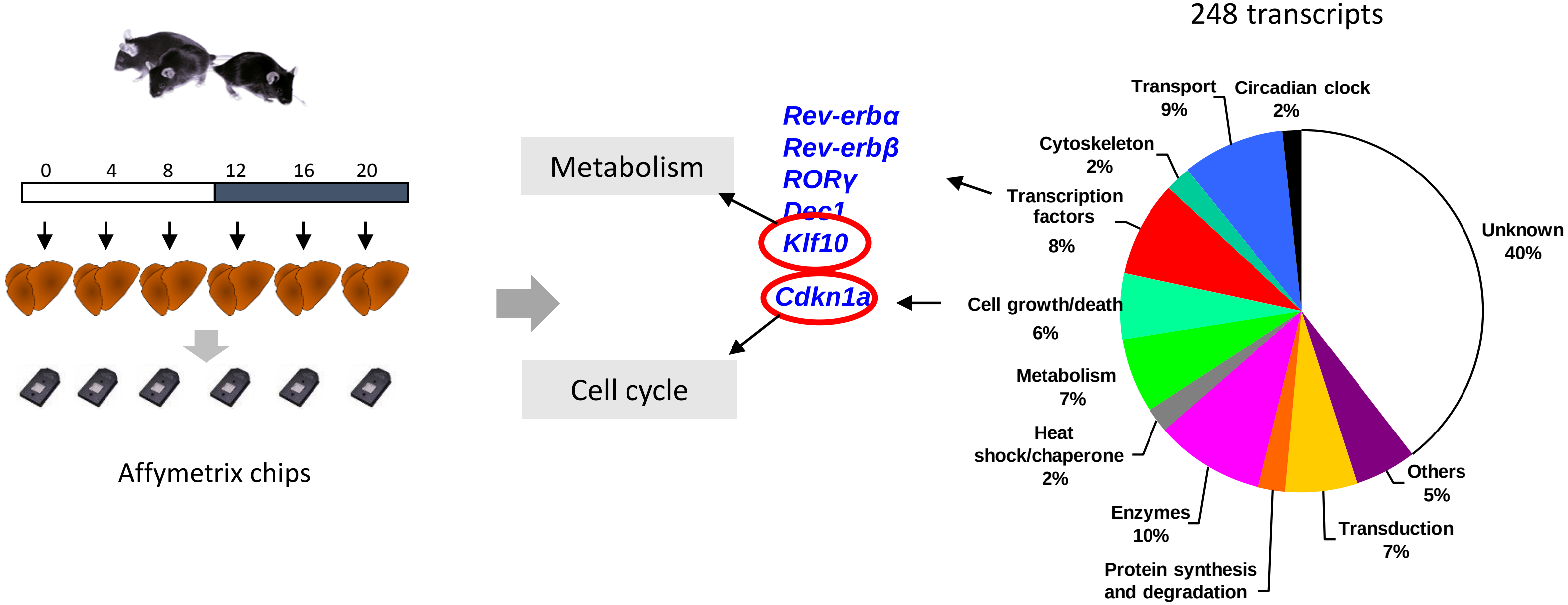




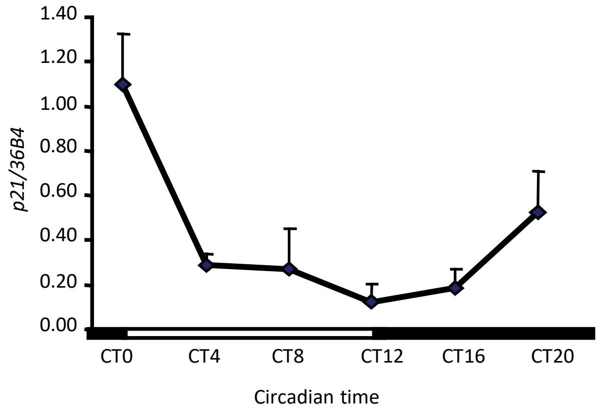
Mitotic genes

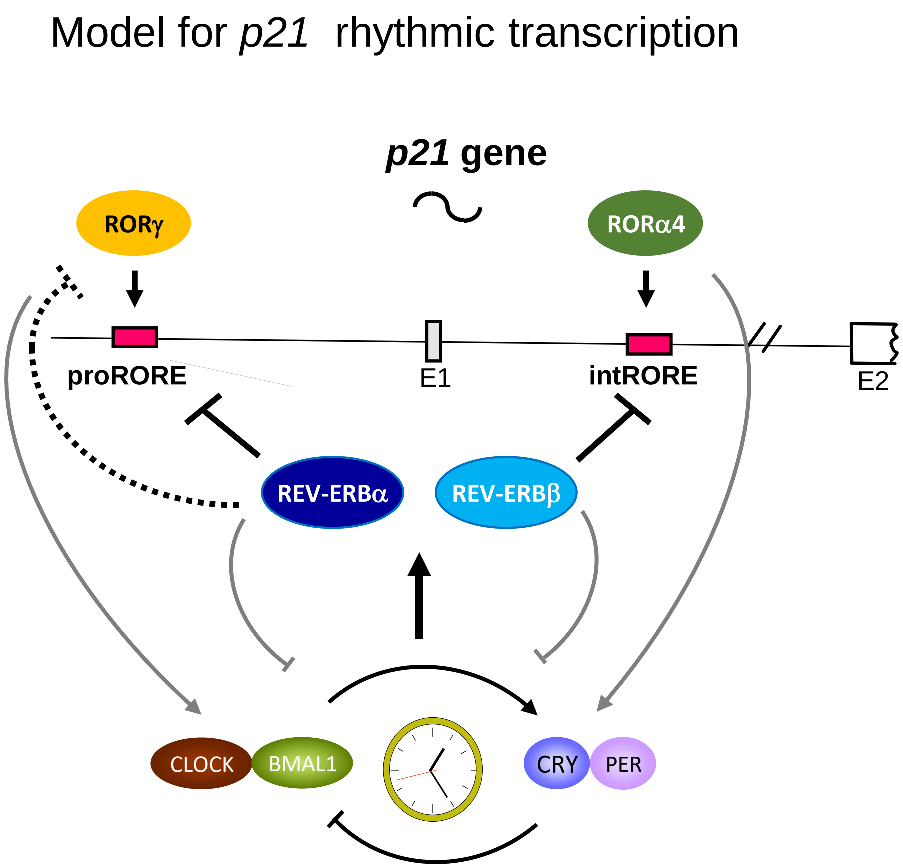
Siffroi-Fernandez et al, Cell Cycle 2014

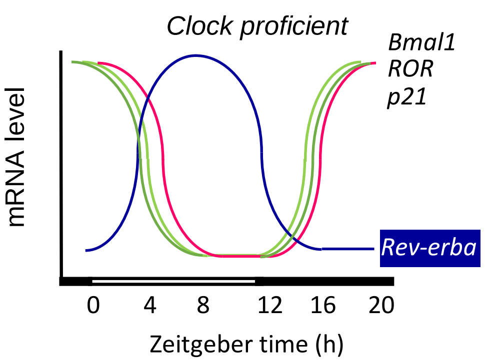
Fishing rhythmic genes in liver

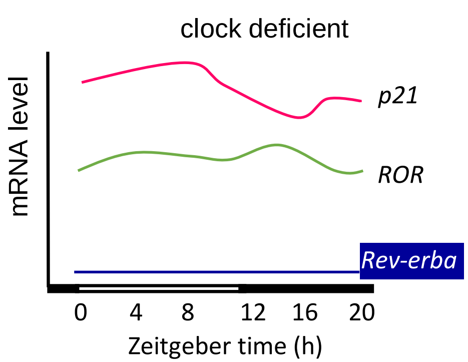


The Rev-ERB/ROR loop drives *p21* oscillations in liver

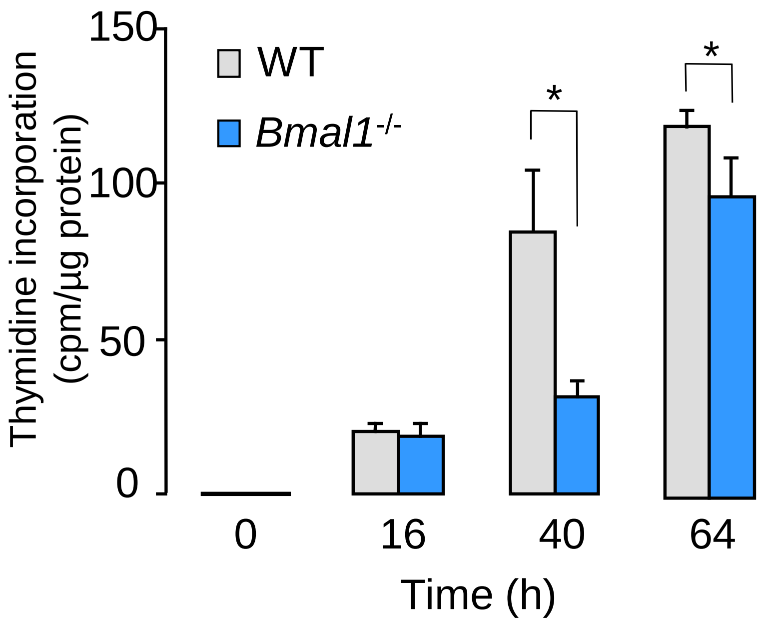


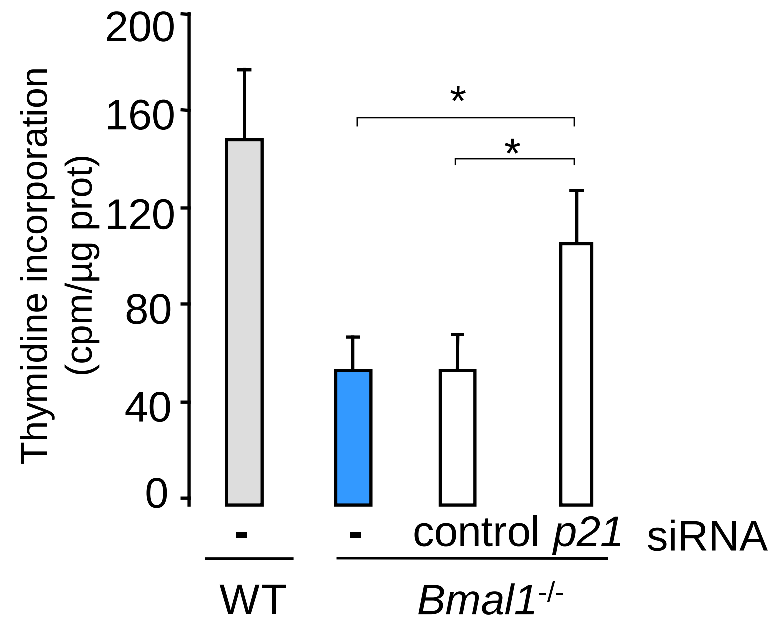


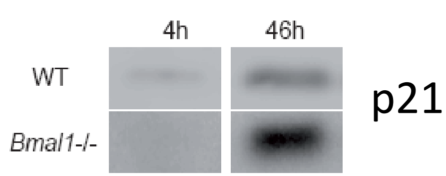




Compromised proliferation of *Bmal1*$^{-/-}$ hepatocytes

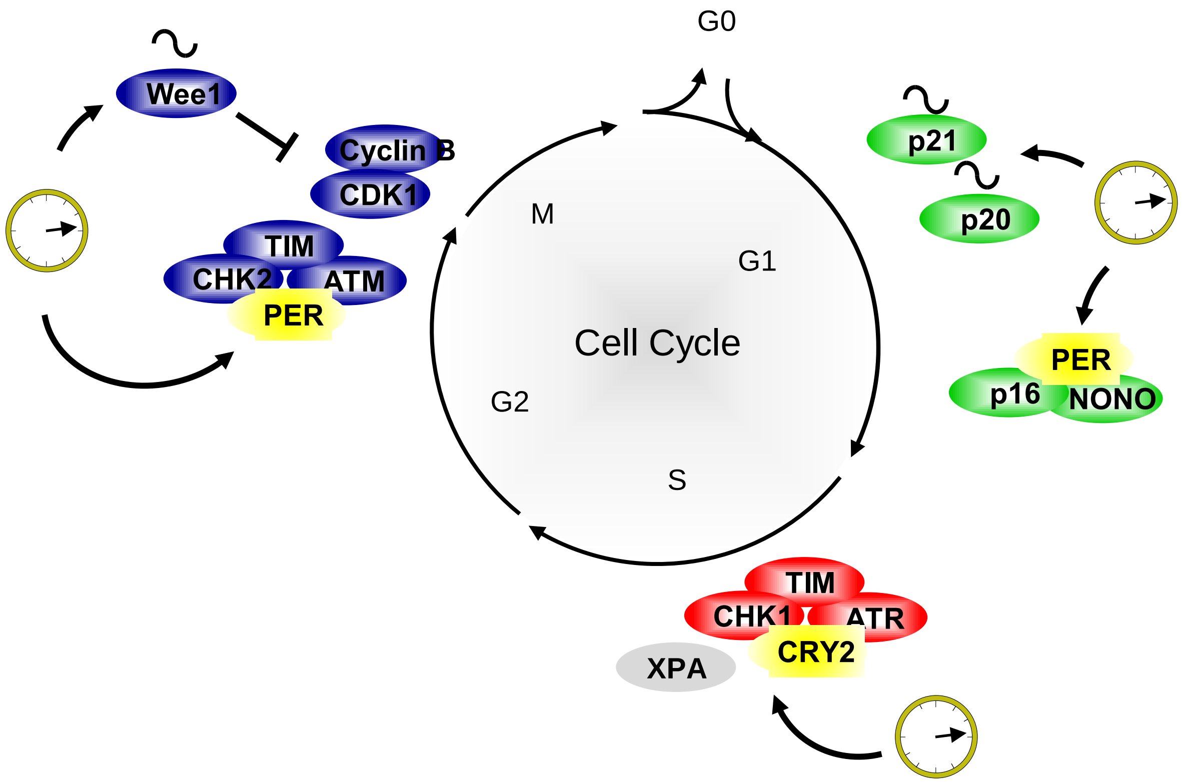






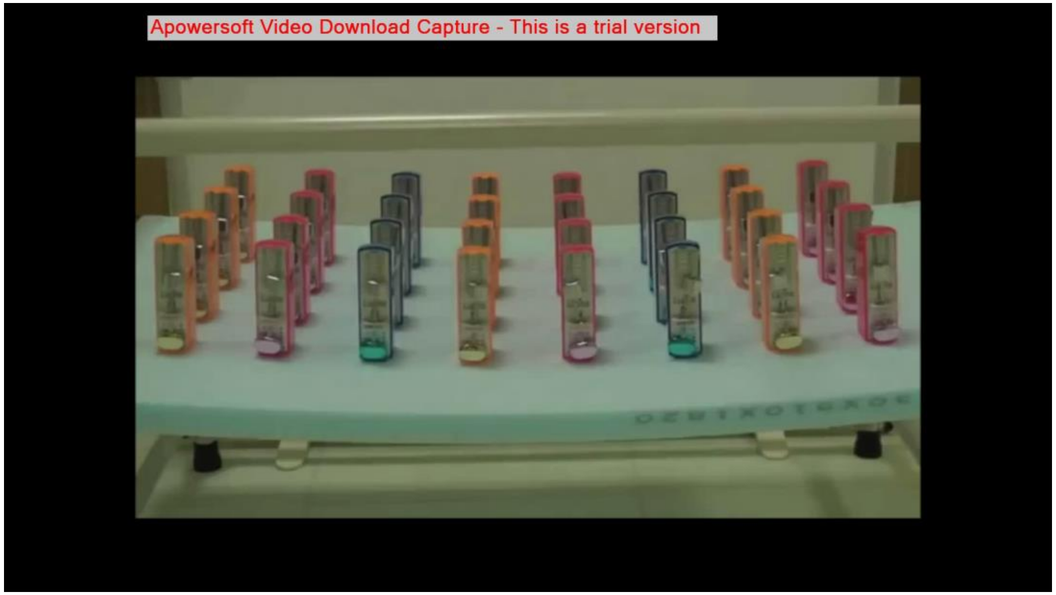
Gréchez-Cassiau et al, JBC 2008

Molecular links between the clock and the cell cycle in vertebrates



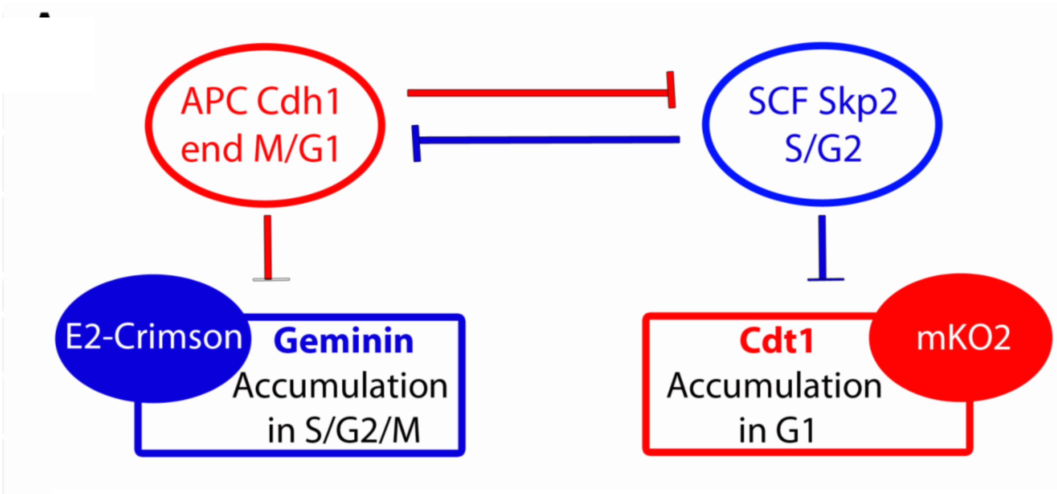
Matsuo et al, Sicence 2003
Geri et al, Cell 2006
Grechez-Cassiau et al , JBC 2008
Kang et al, PNAS 2010
Kowalska et al, PNAS 2013

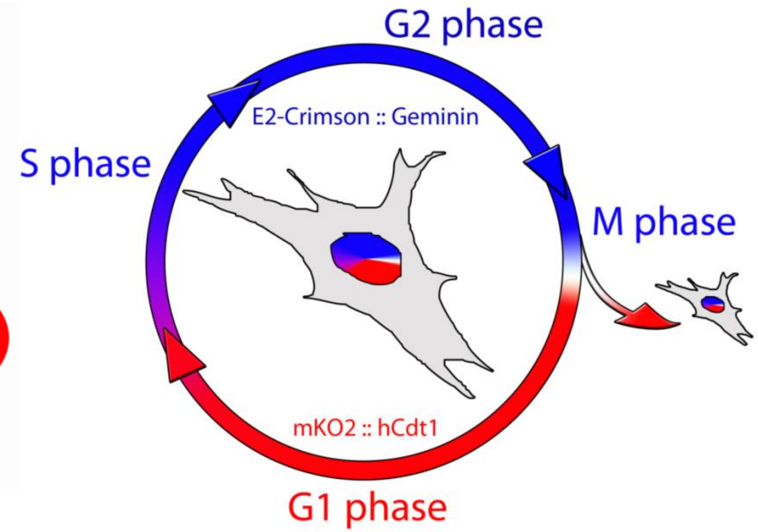
Are the mammalian cell cycle and clock coupled oscillators ?

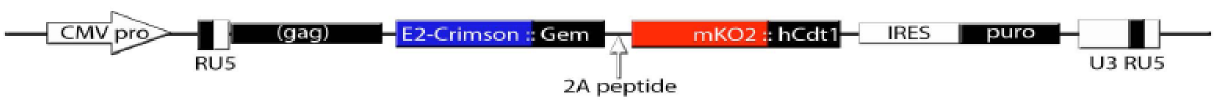


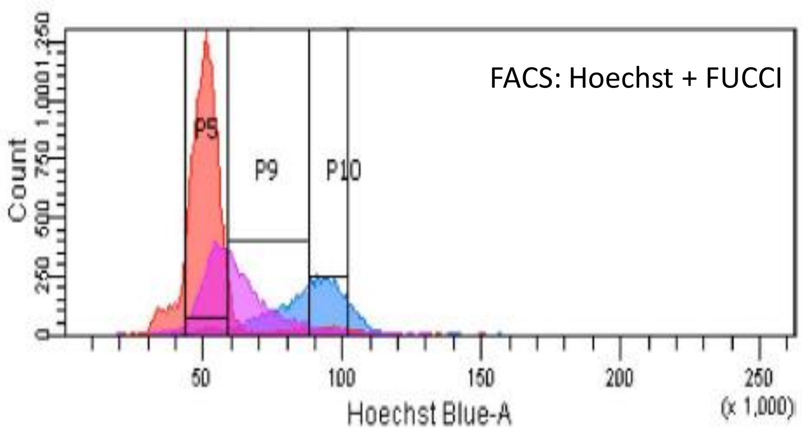
- Can we demonstrate experimentally this coupling ?
- What is the coupling mode ?
- How is coupling influenced by external perturbations ?
- Build mathematical models to better understand the behaviour of the coupled system ?

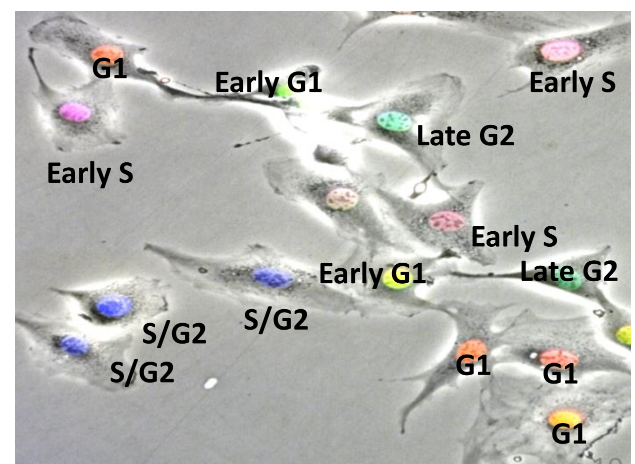
Monitoring of the entire cell cycle progression in single cells using FUCCI









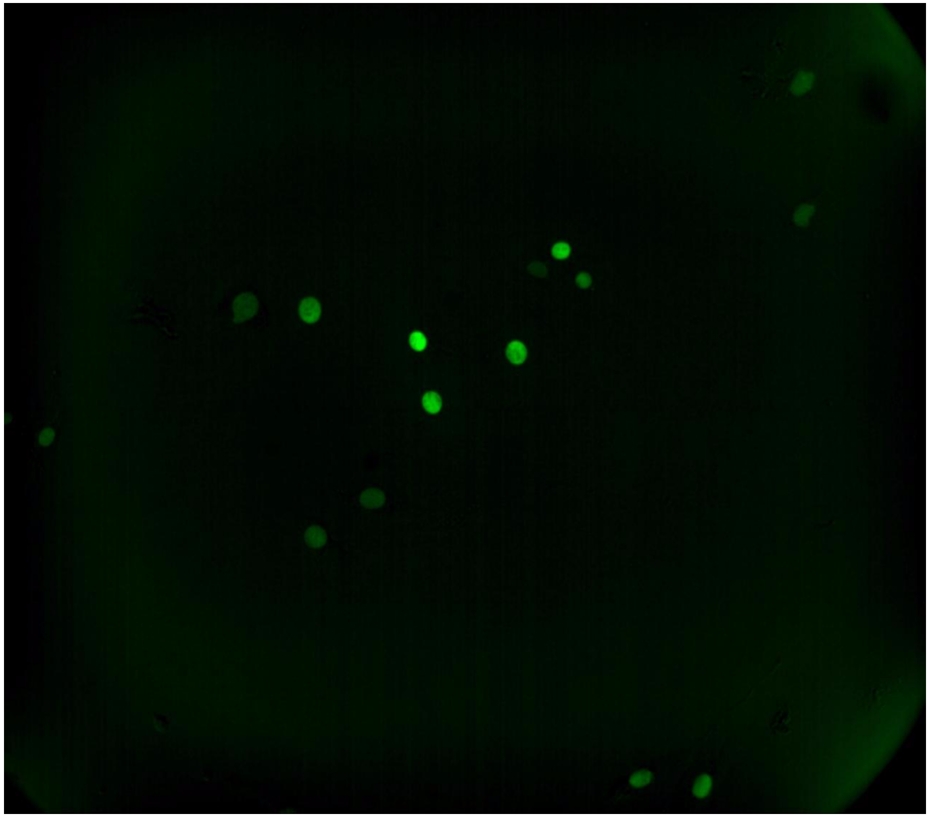


Sakaue-Sawano et al, Cell 2008

Visualizing the dynamics of the clock and the cell cycle in single cells

NIH3T3-RVNP

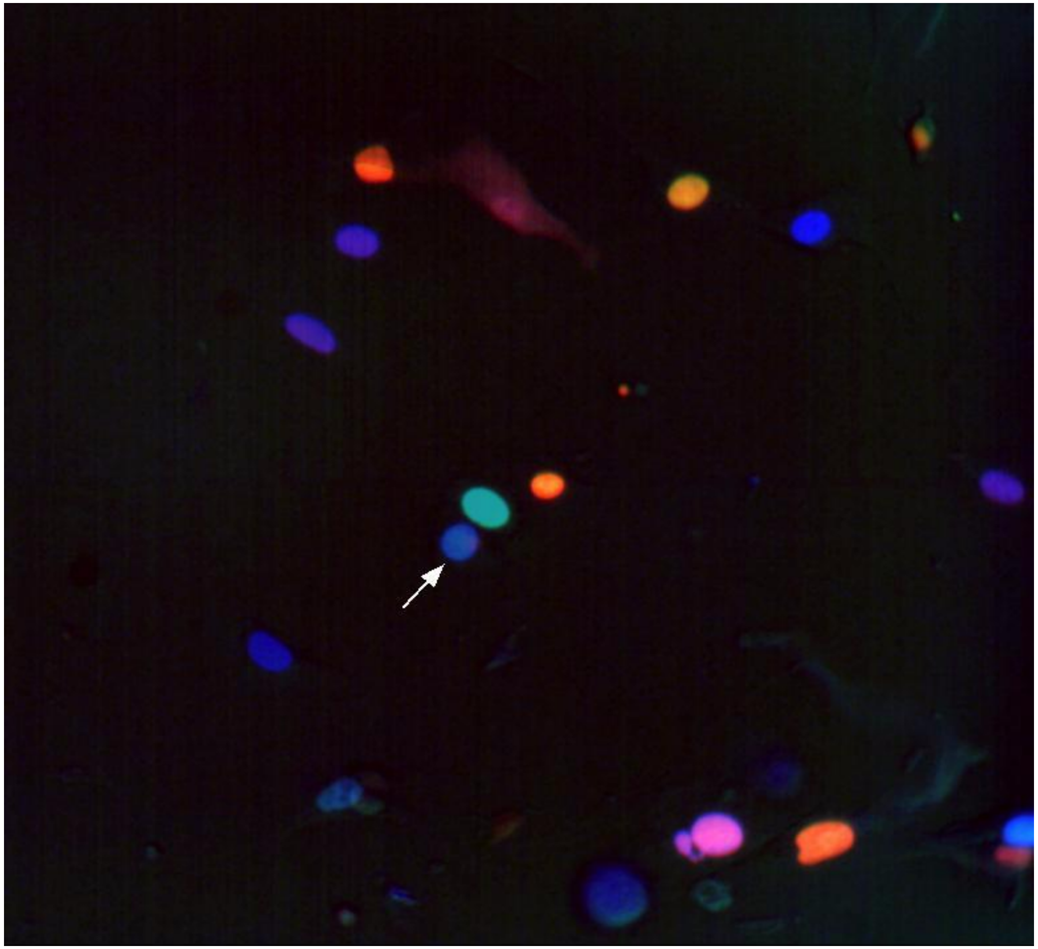
- Live cells
- Single cells
- Real time
- High temporal resolution (min)
- Spatial Information
- Variability



Nagoshi et al, Cell 2004
Feillet et al , PNAS 2014

Visualizing the dynamics of the clock and the cell cycle in single cells

NIH3T3-RVNP+FUCCI



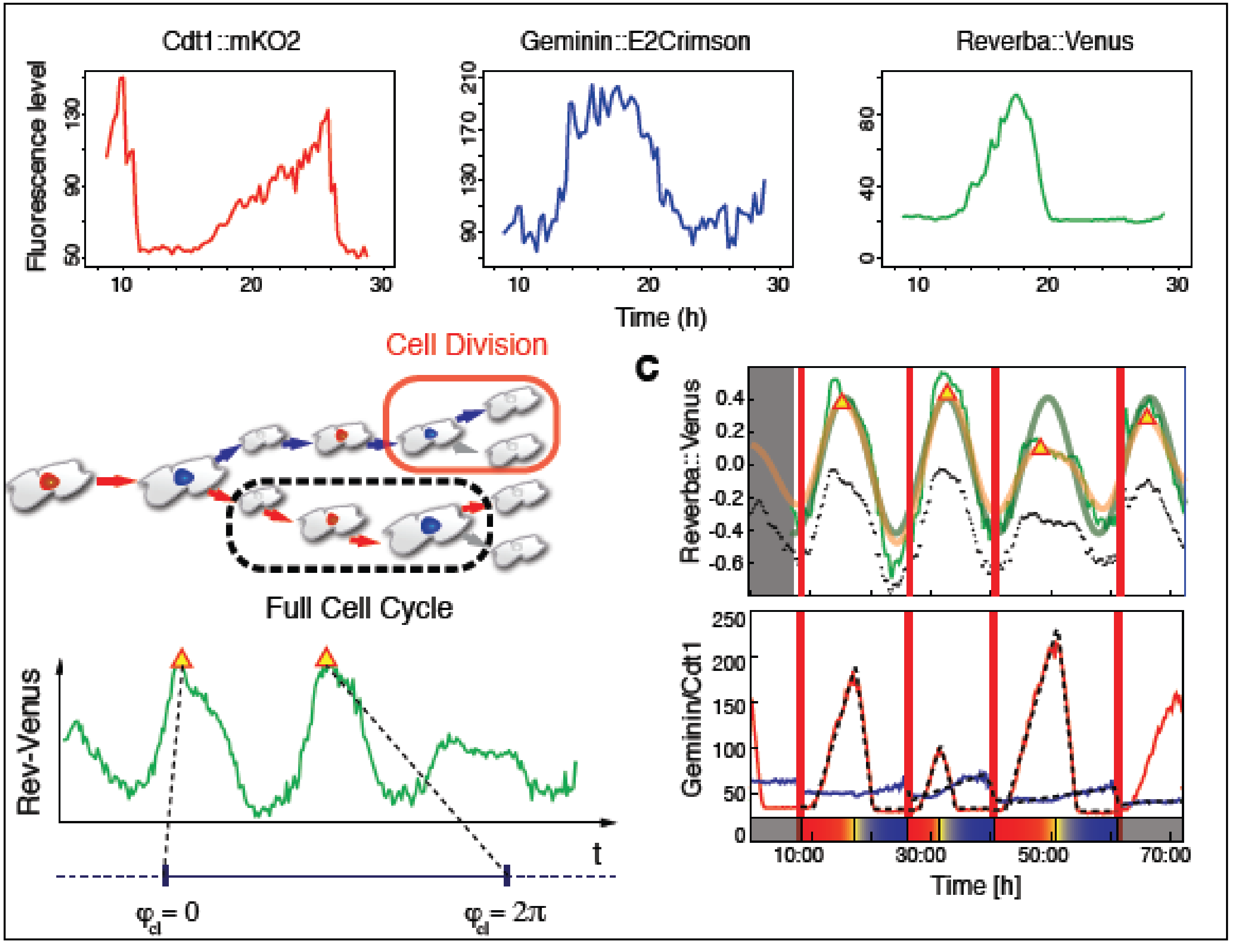
Nagoshi et al, Cell 2004
Feillet et al , PNAS 2014

From images to global phase dynamics of lineages

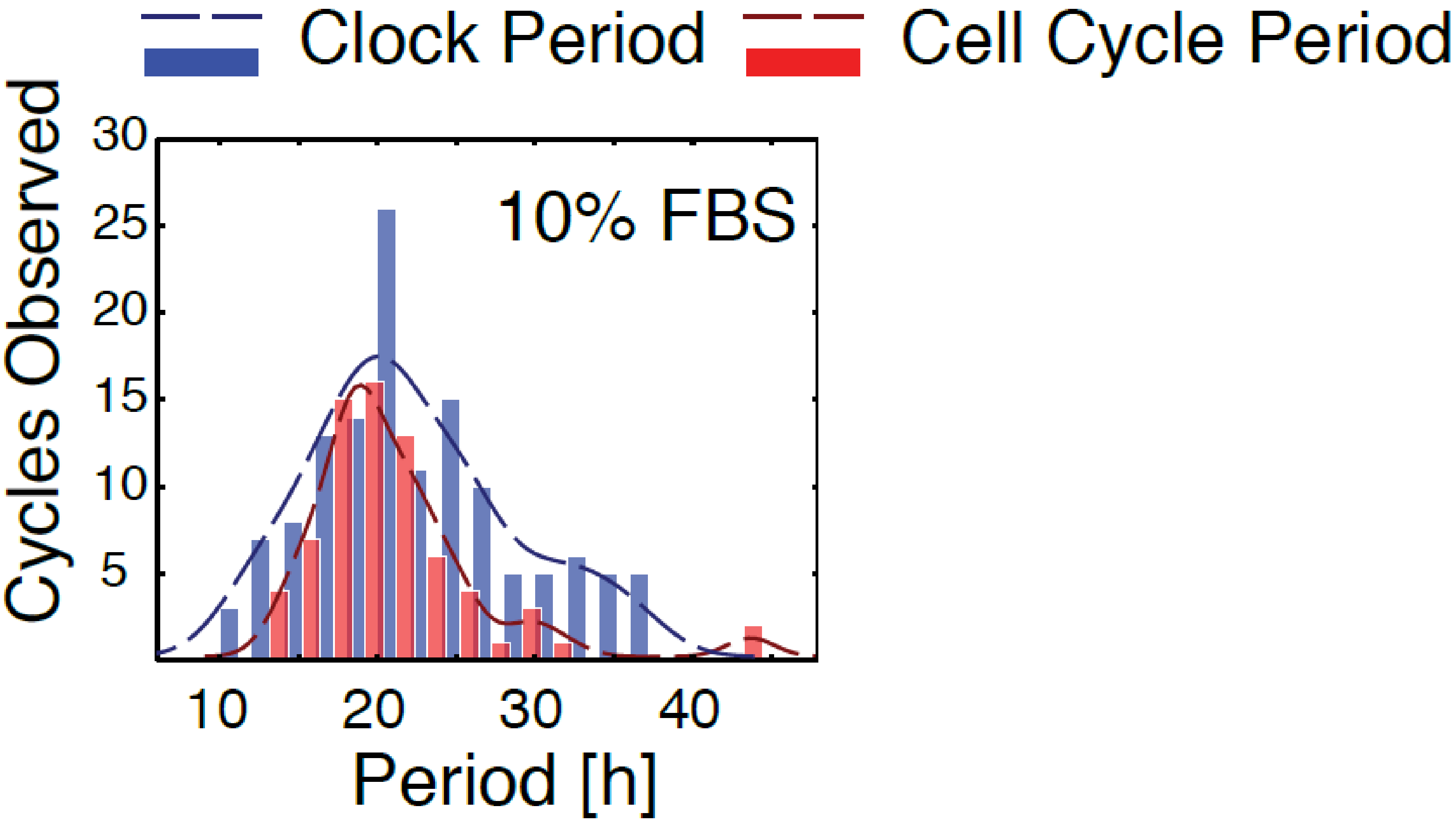
Lineage tracker 2.0 (Fiji)

- Spectrum resampling (clock)
- Piecewise linear model (t_a, t_b, t_c) (cell cycle)

- 344 lineages
- 1709 cells
- 3551 cell cycles
- > 10^6 datapoints
- > 2 To

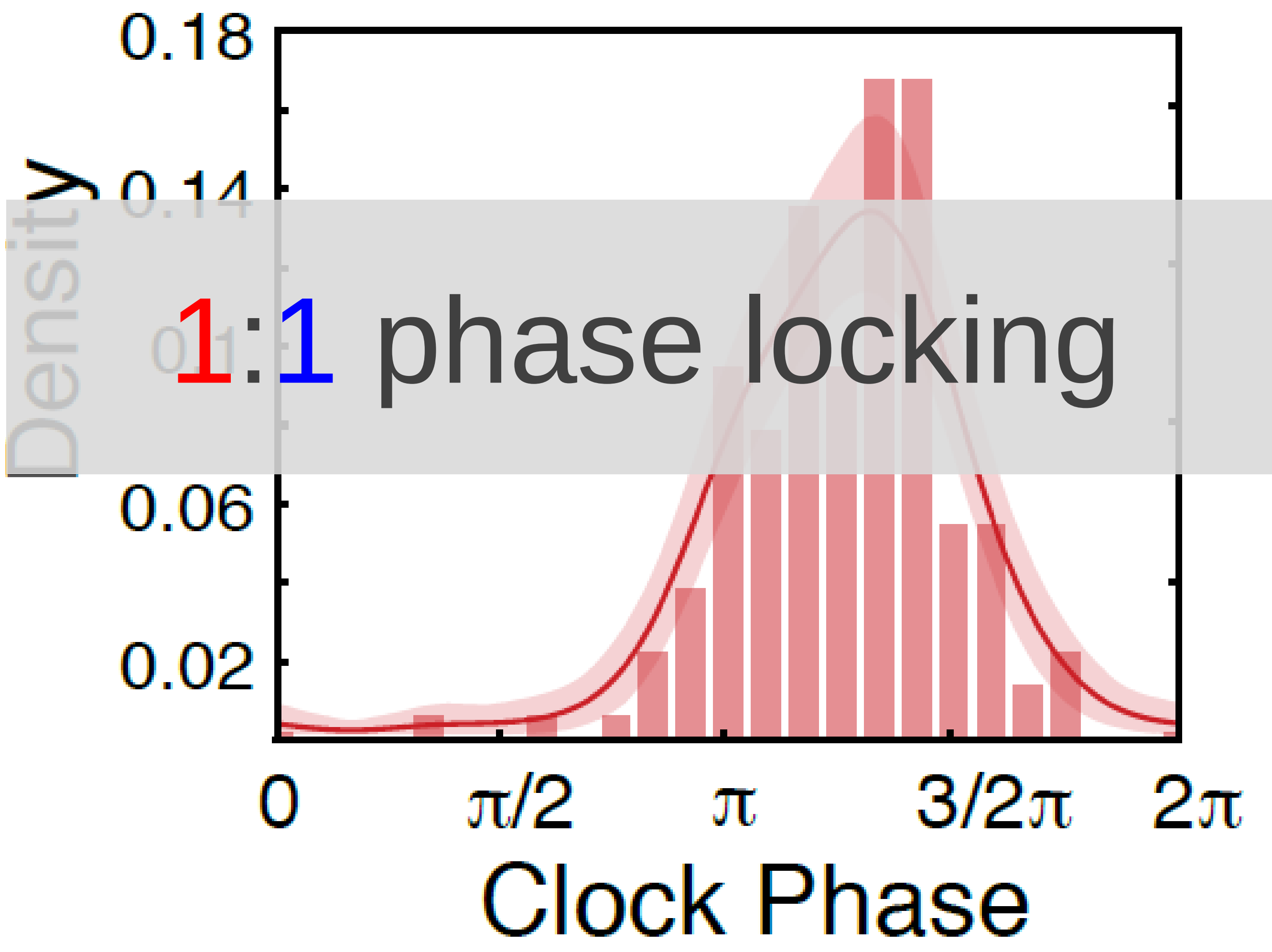


The clock and the cell cycle oscillate at similar periods in unsynchronised cells



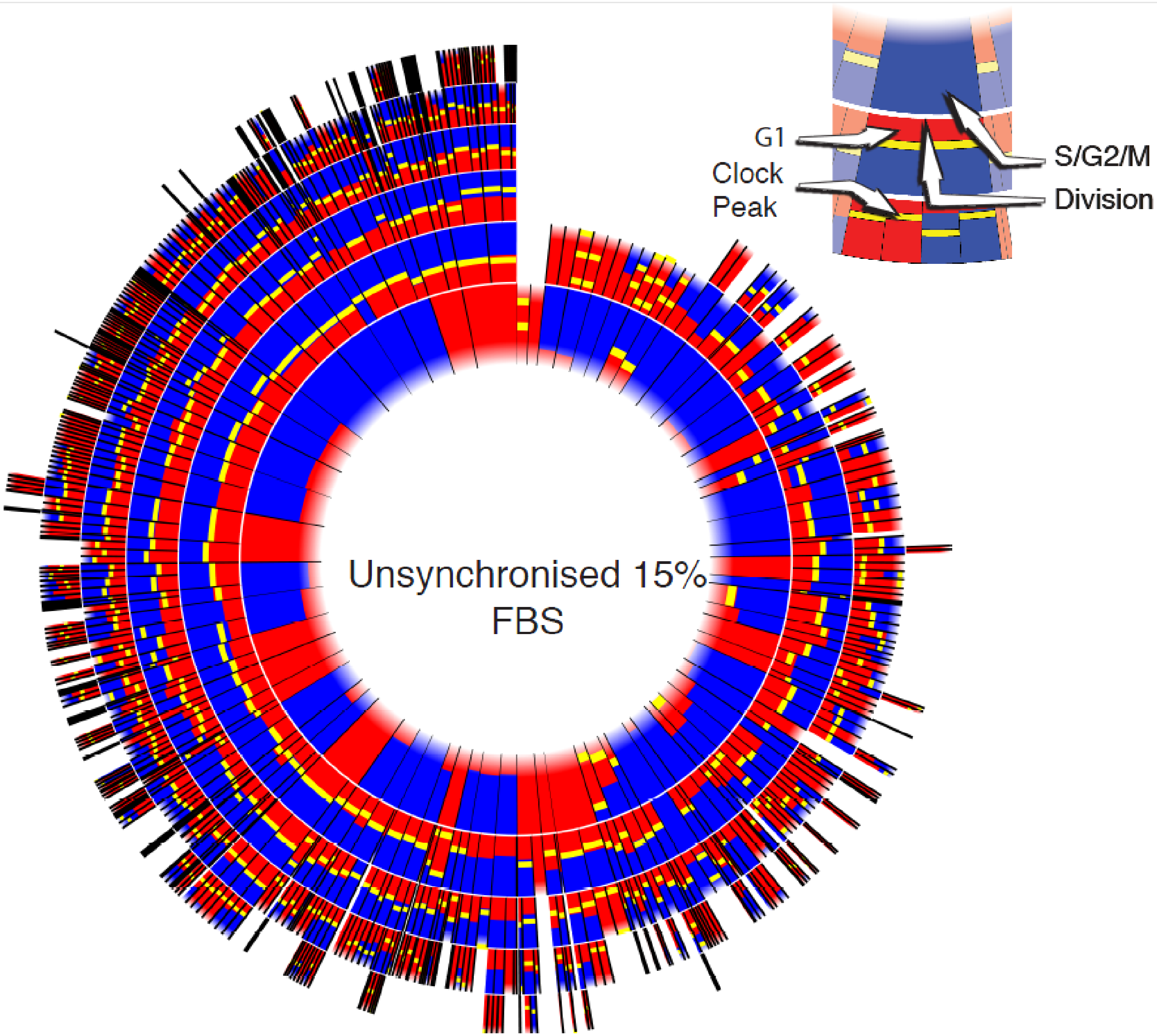
Clock: 21.9 ± 1.1 h
Cell cycle: 21.3 ± 1.3 h

A fixed phase relationship between the clock and the cell cycle

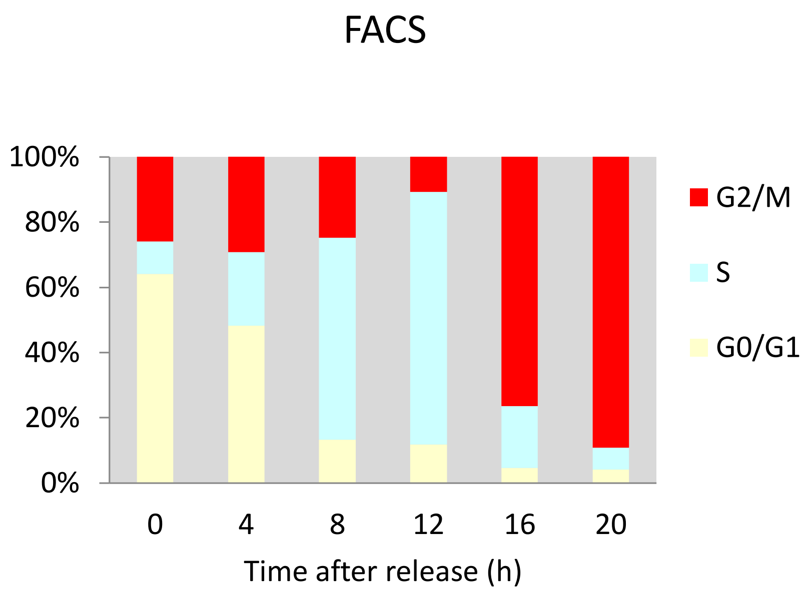


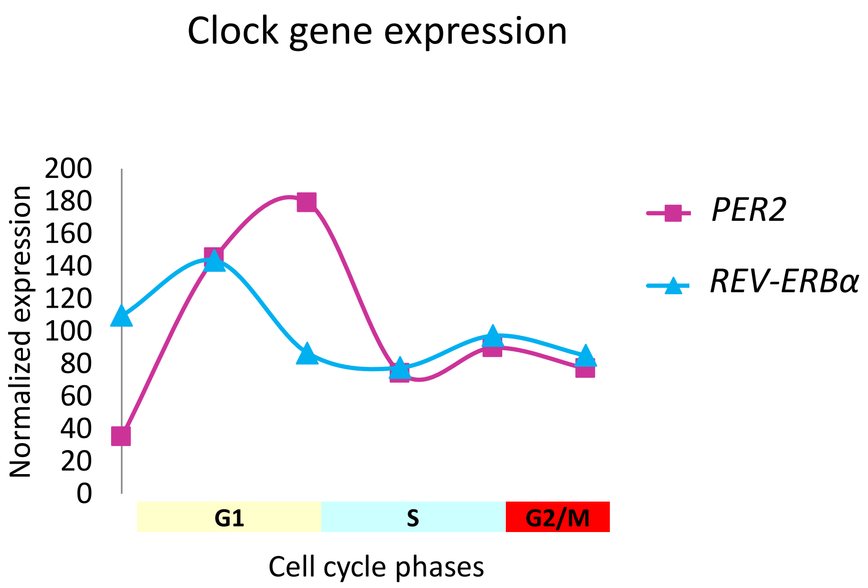
Mean clock phase at division: 3.97 ± 0.14 radians

The clock and the cell cycle display a fixed phase relationship across generations

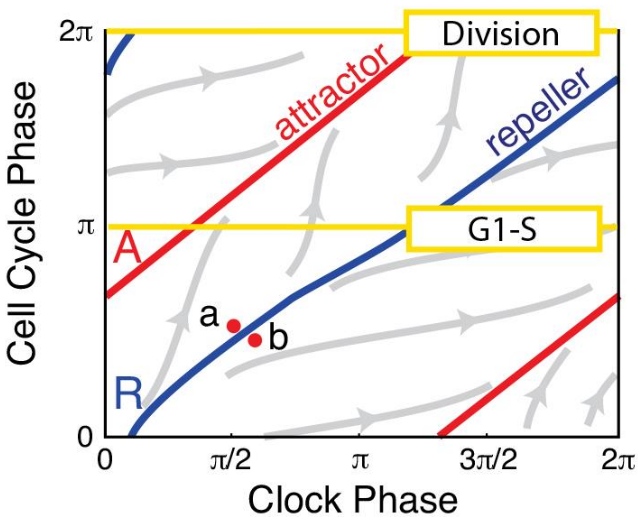


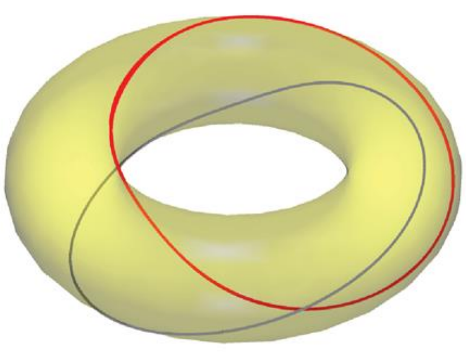
Cell cycle phase dependent expression of *Rev-erbα* and *Per2* in human HaCaT skin cells

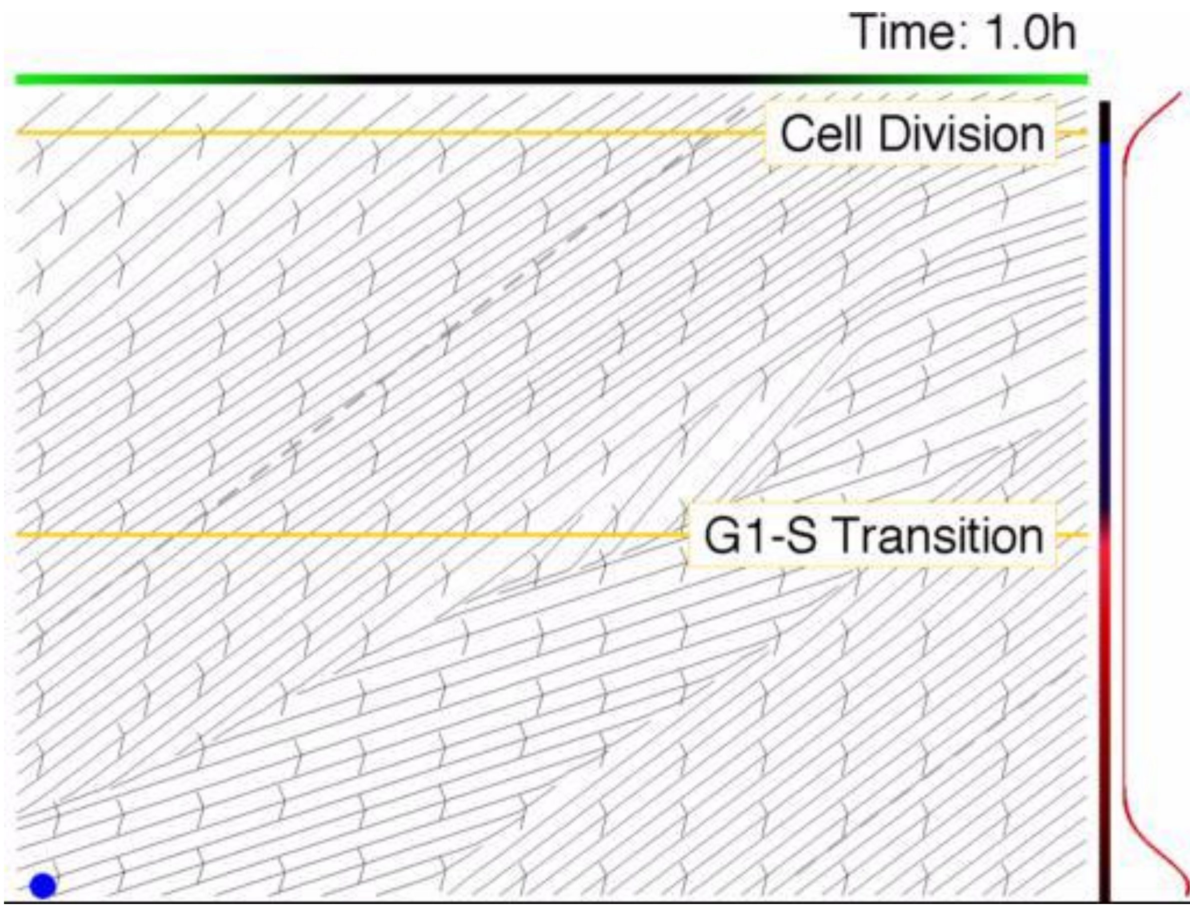




Joint trajectory for a 1:1 phase-locked system

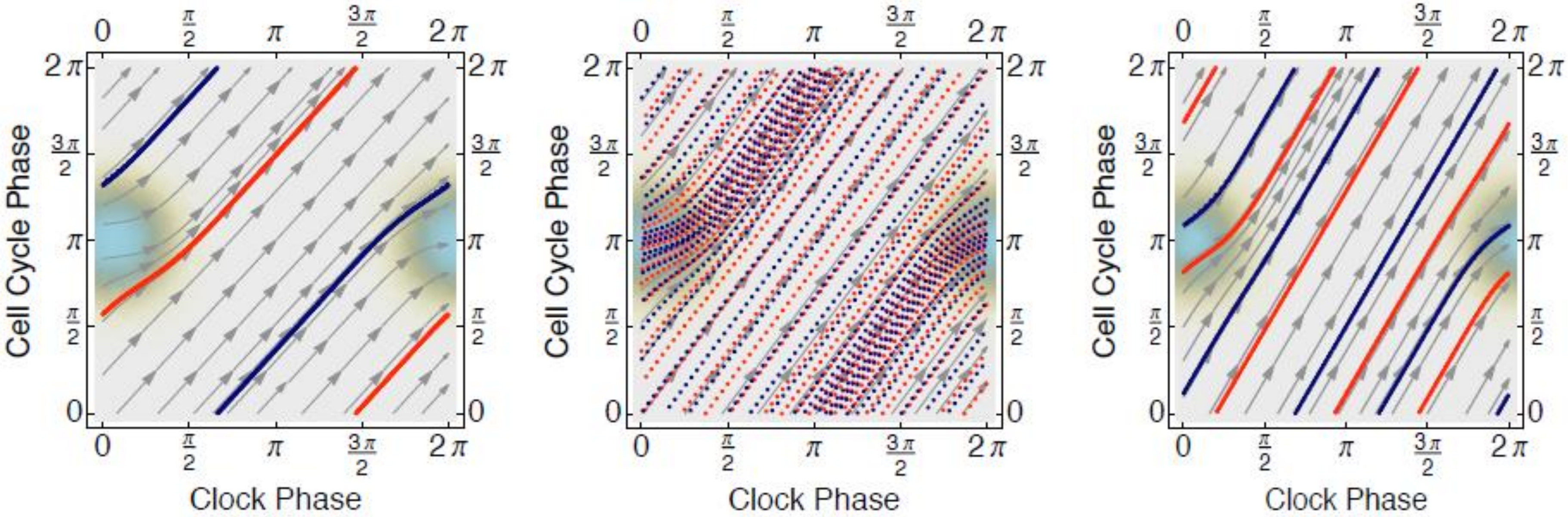






One single coupling region can explain different regimen

1:1 5:4 3:2



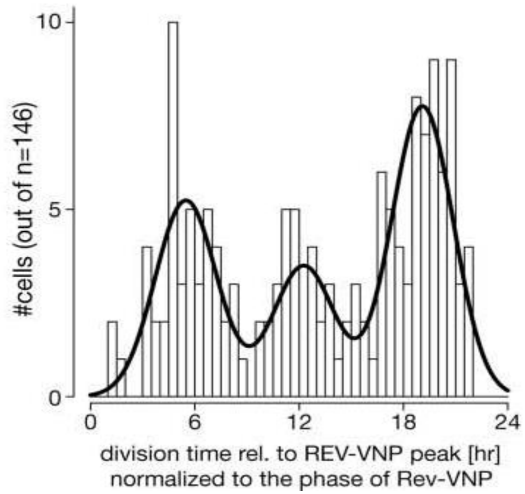
15 % FBS

10 % FBS + dex pulse

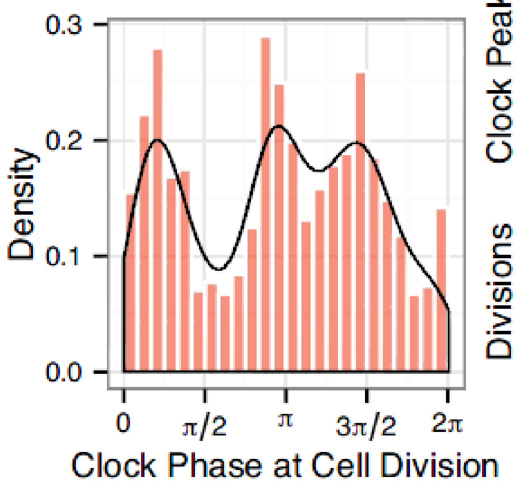
20 % FBS + dex pulse

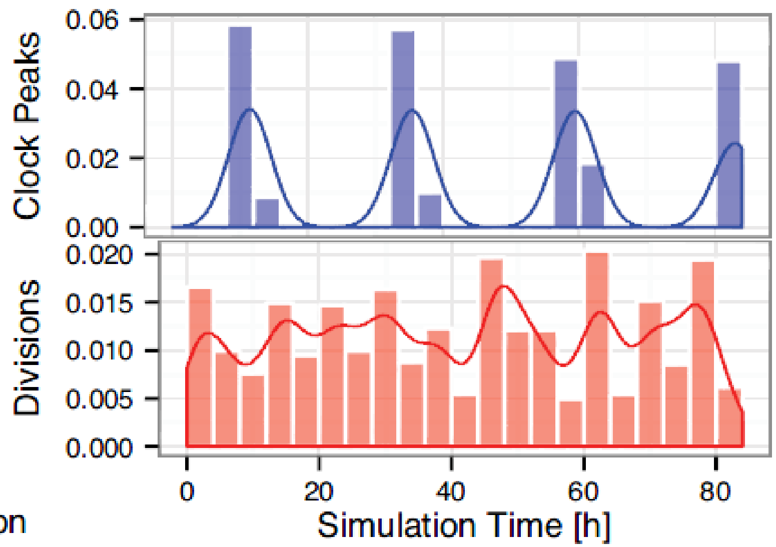
Simulation of a 3:2 coupling ratio

- NIH3T3-RVNP
- Dex pulsed cells
- 20 % FBS



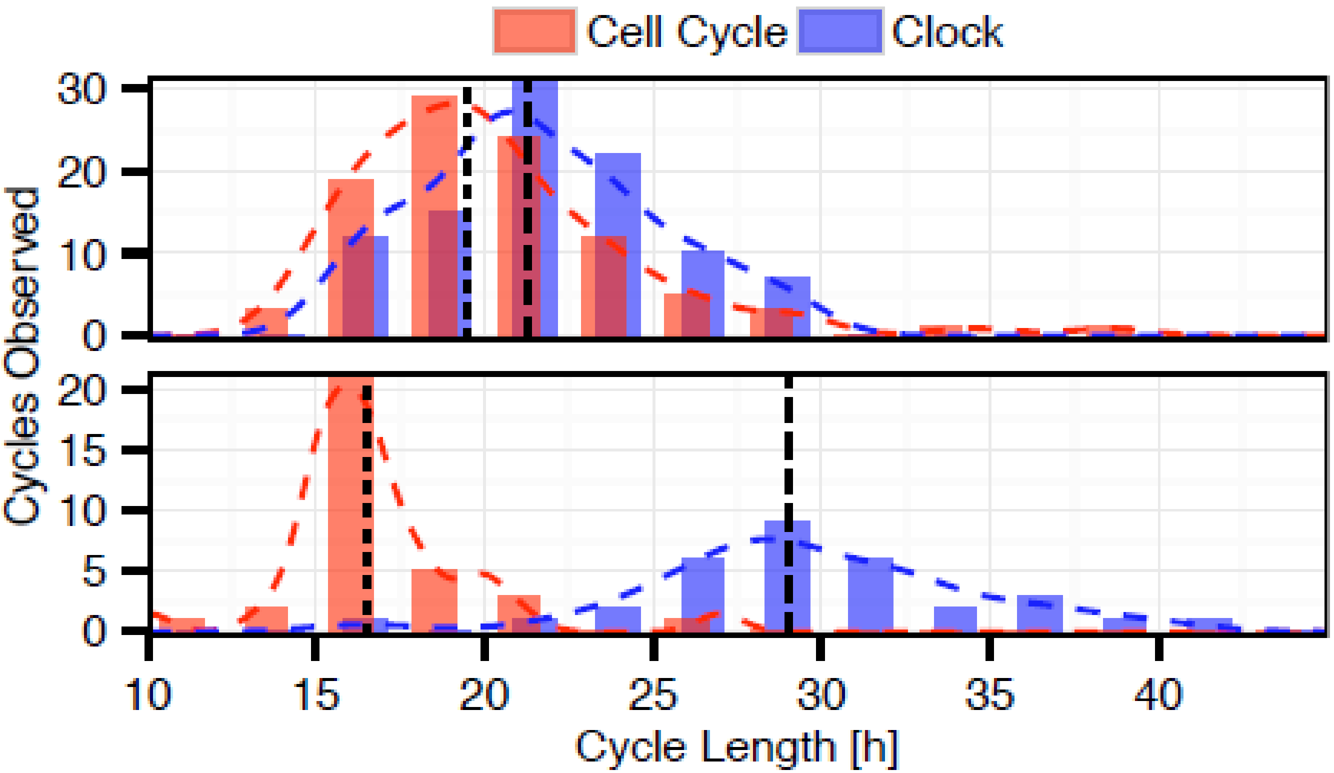
Nagoshi et al Cell 2004



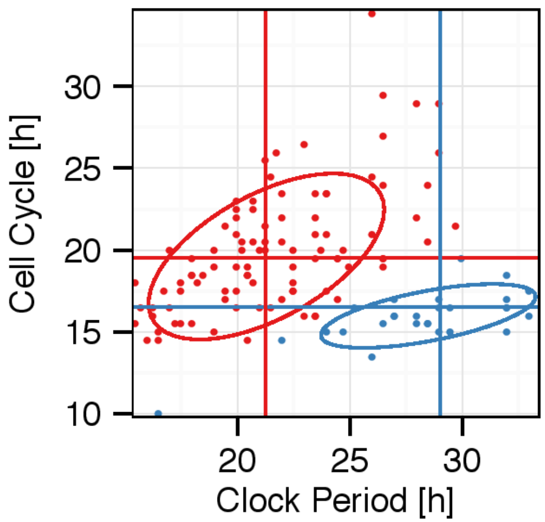


Two coexisting coupling regimes in synchronized cells cultured in 20 % FBS

NIH3T3/20% FBS/Dex

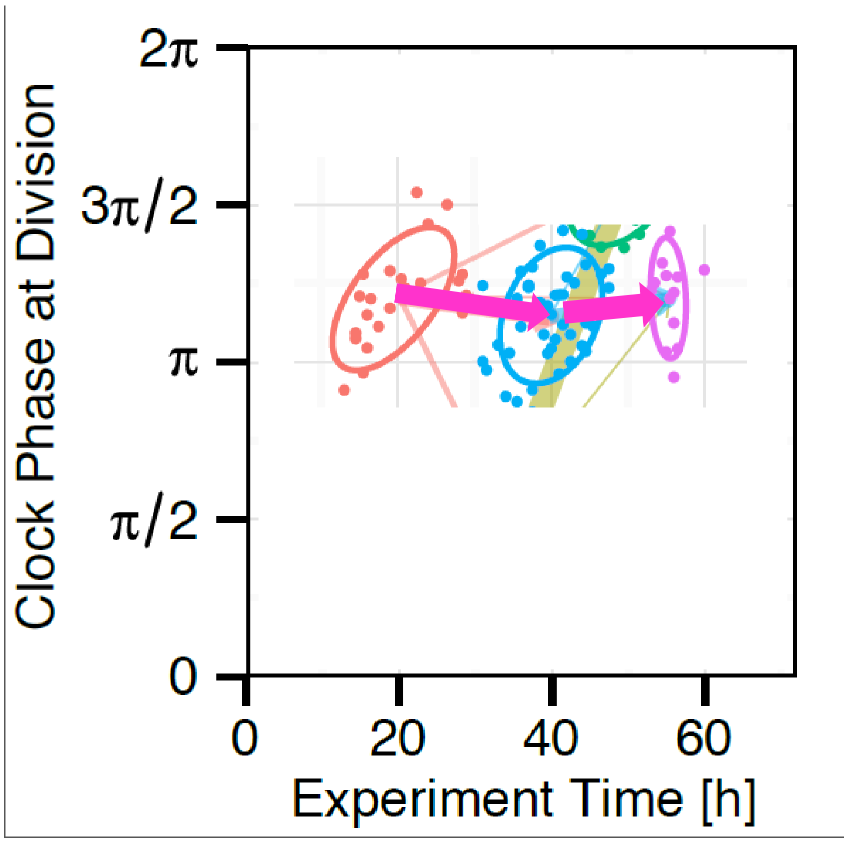


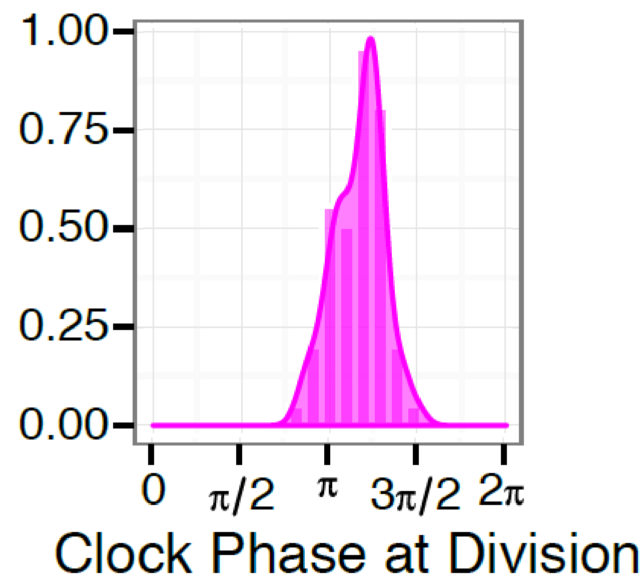
Clustering by clock/cell cycle period ratios



Clustering analysis in 20 % FBS

Population A (1:1 ratio)
Clock phase at division *vs* experiment time

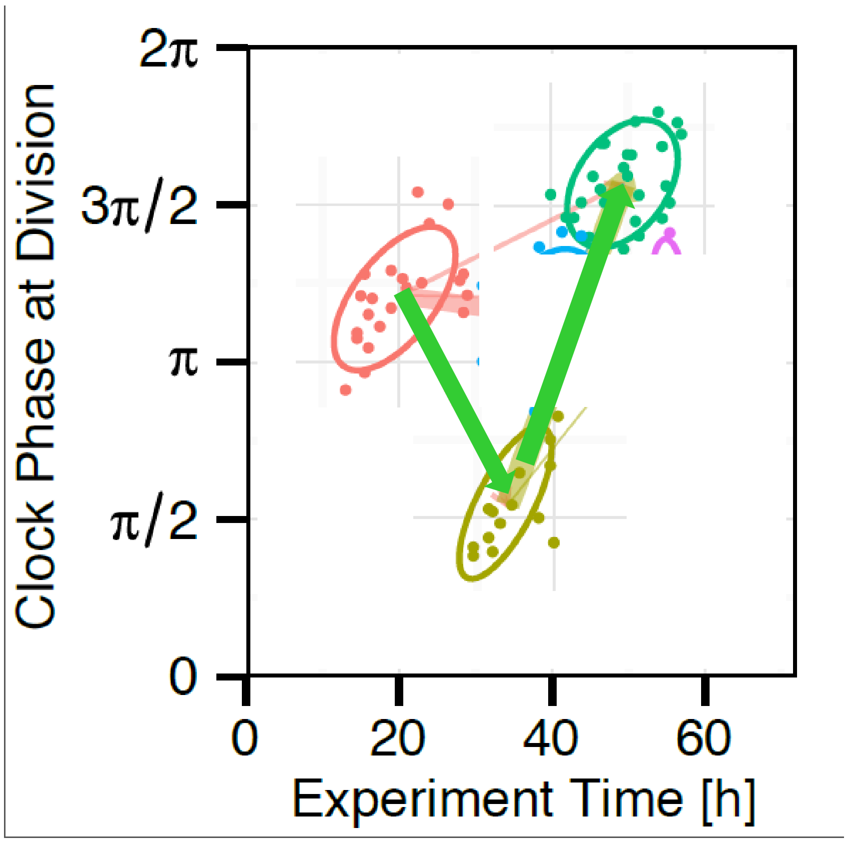


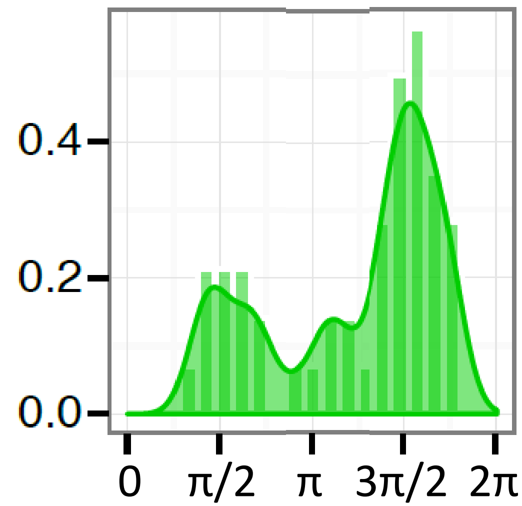


Clustering analysis in 20 % FBS

Population B (3:2 ratio)
Clock phase at division *vs* experiment time

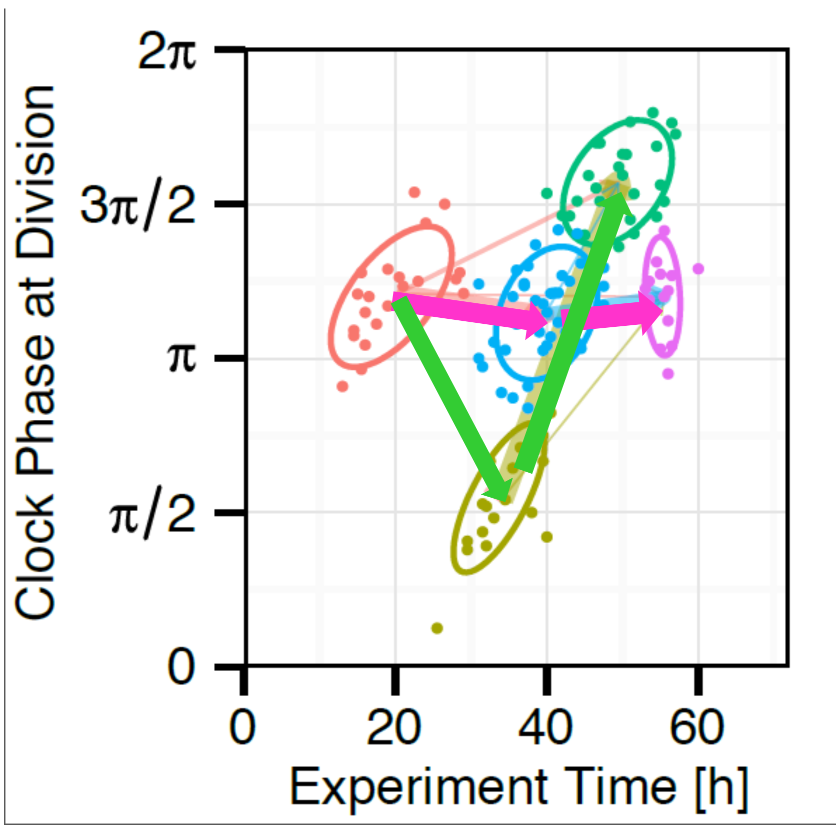
=> 3 clock phases at division

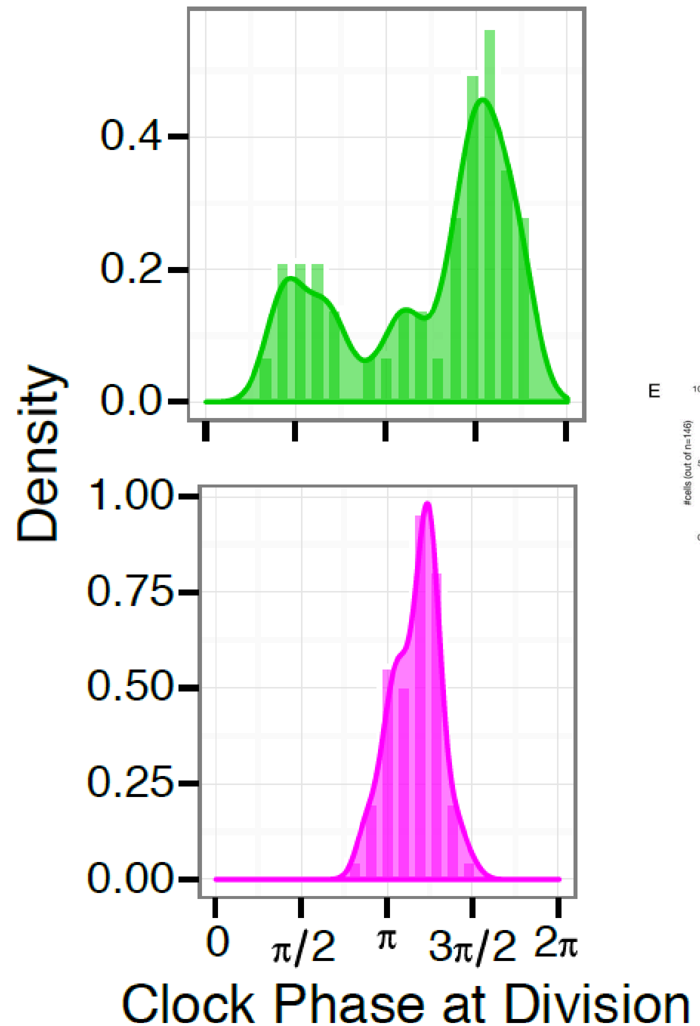




Clustering analysis in 20 % FBS

Populations A + B (1:1 + 3:2 ratio)
Trimodal distribution





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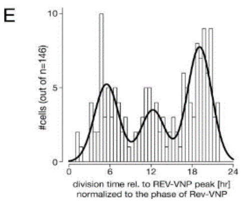
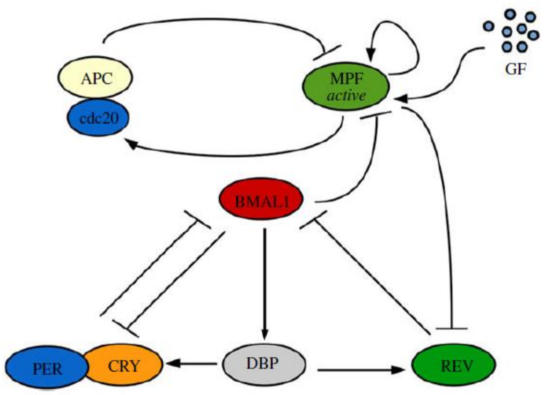
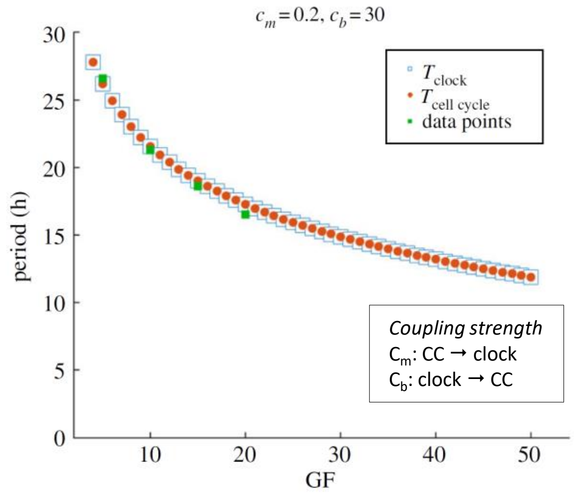


Modelling the the bidirectional coupling of the clock-cell cycle system

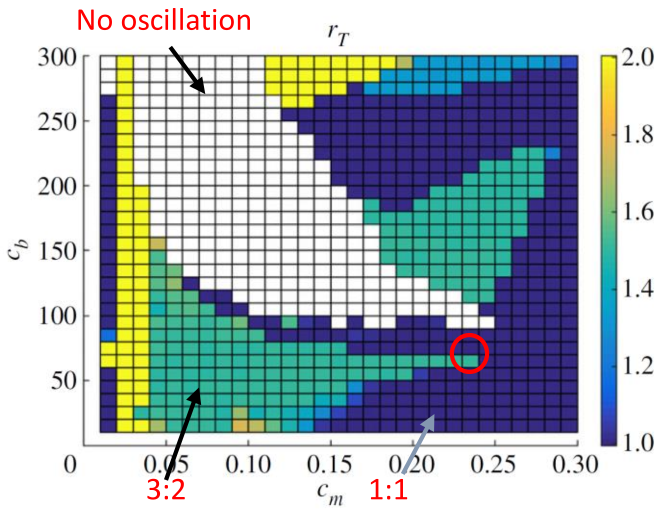
Bidirectional model



Period response

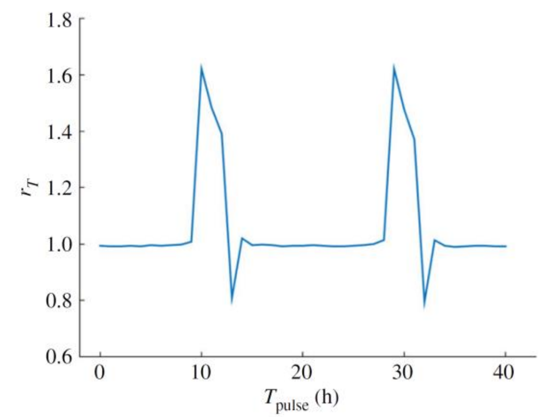


Systems's synchronisation



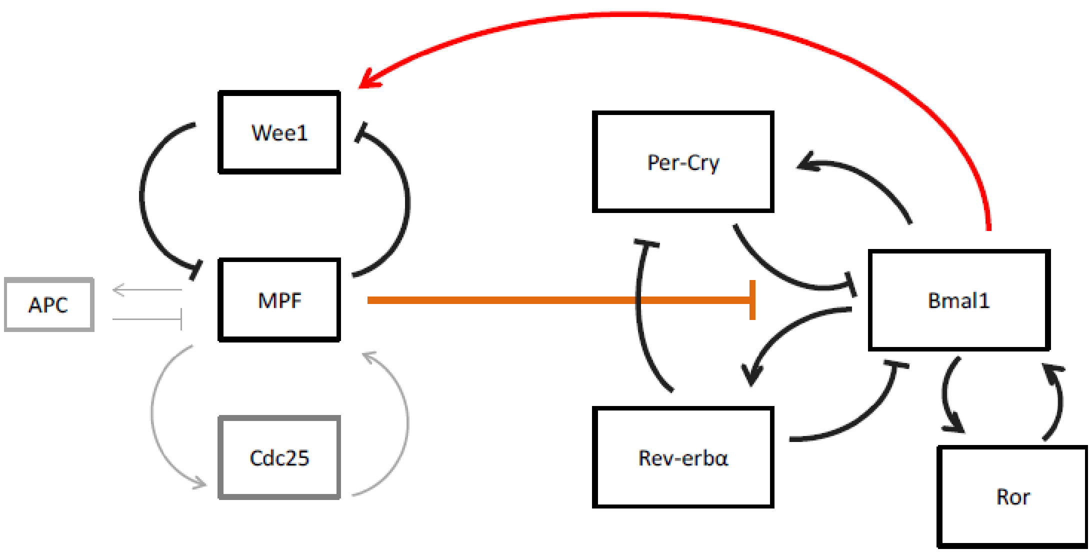
GF = 20

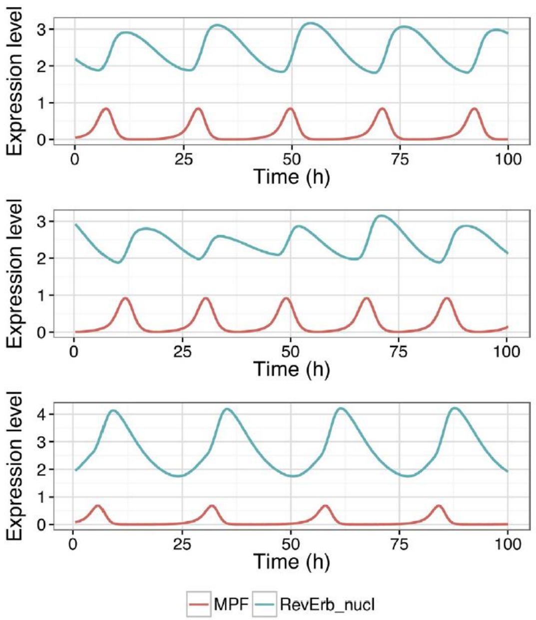
Response to Dex pulse



Almeida et al JTB 2020
Almeida et al RSOS 2020
Almeida et al JBCB 2020

Role of G2/M in the circadian clock-cell cycle coupling





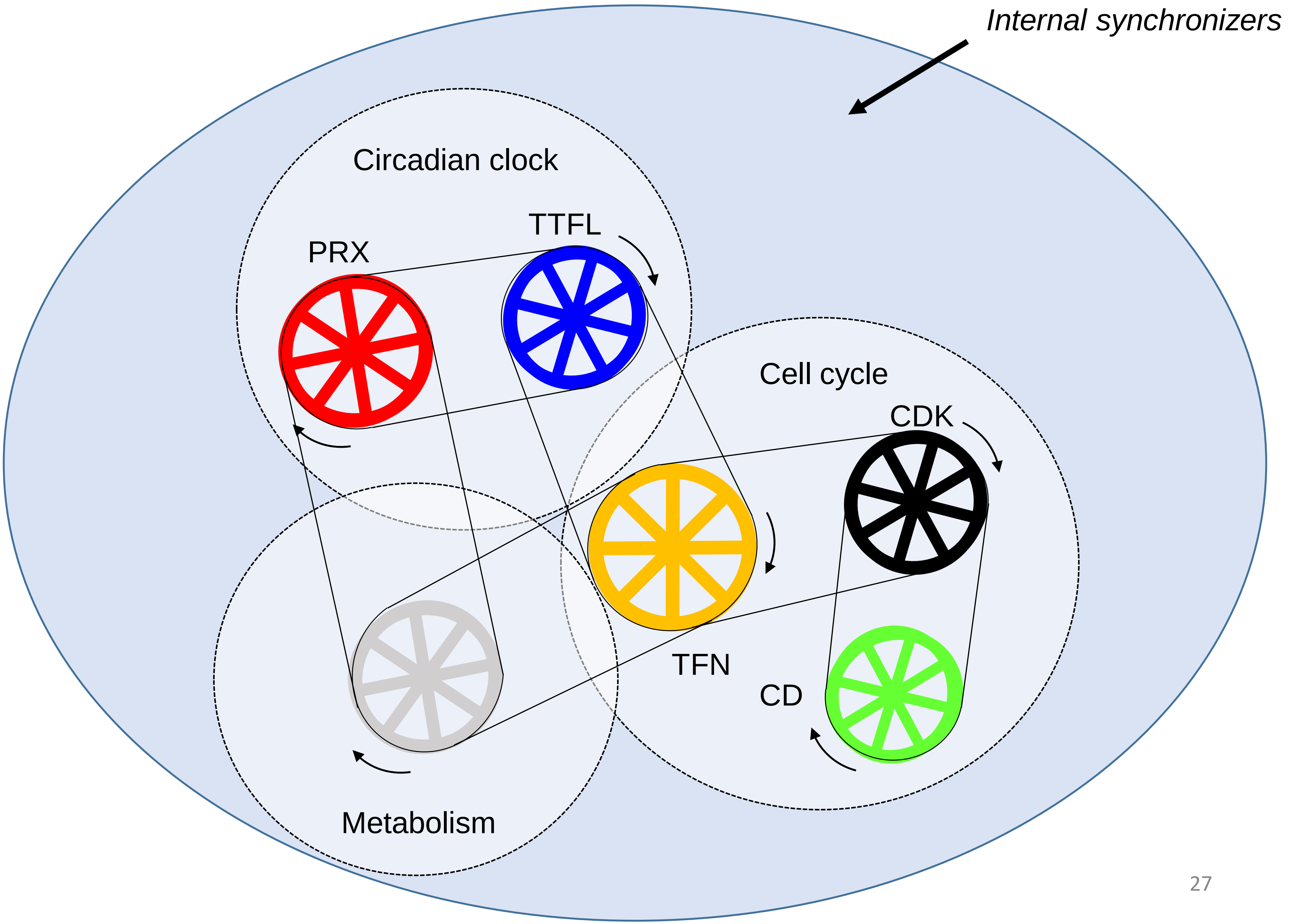
21.3 h

20.6 h

26 h

Traynard et al, Biosystems 2016

Phase locking to coordinate multiple oscillators in cells



Conclusion

- Multiple molecular links between the clock and the cell cycle
- The cell cycle has a significant influence on the clock in unperturbed mammalian cells
- A robust phase-locking mechanism
- Bidirectional model explains the differetial dynamics of Dexamthasone pulsed dividing cells (*S Almeida & M Chaves*)
- Modelling suggests a role for *Bmal1* inhibition around G2/M for period and phase control (*P Traynard & F Fages*)