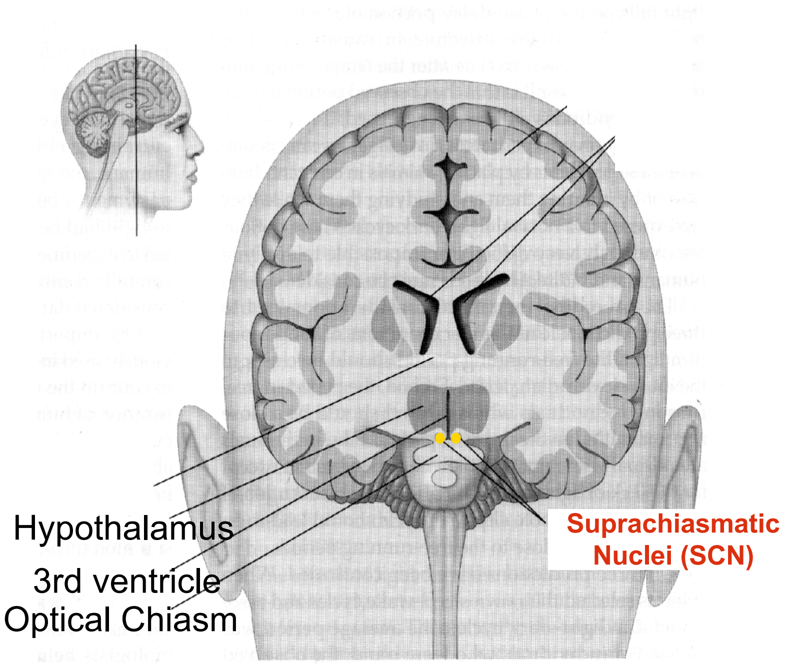
Mammalian circadian clock

Mammalian circadian clock

Suprachiasmatic nucleus (SCN)



- SCN = circadian pacemaker
- Located in the hypothalamus
- Receives light signal from the retina
- Contains about 10000 neurons

Molecular mechanism

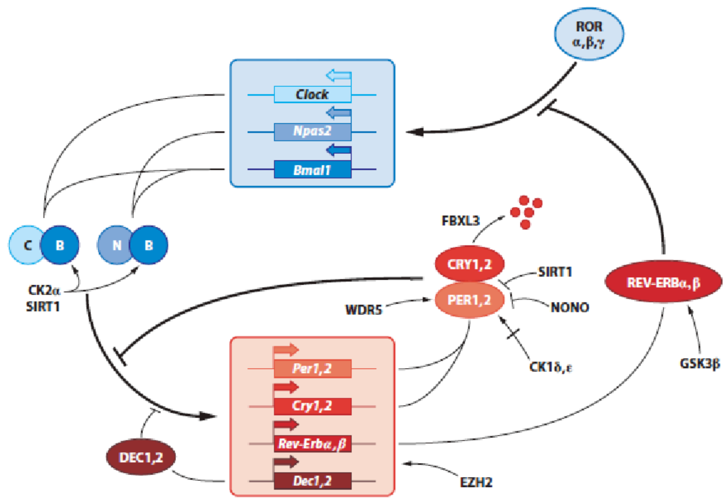
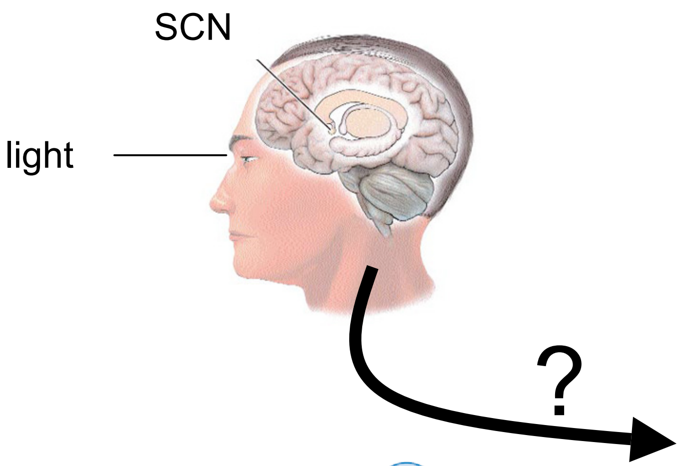


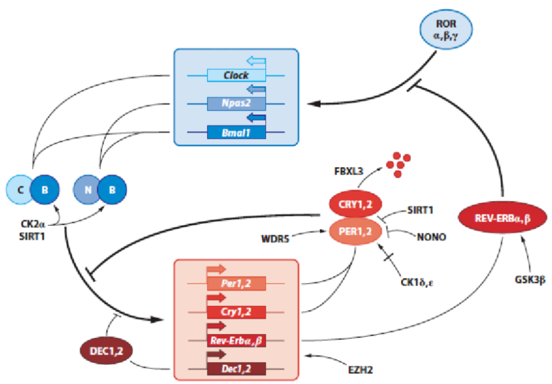
Figure from Lévi *et al* (2010) *Annu Rev Pharmacol Toxicol*. 50:377-421.

- Circadian oscillations are generated at the level of single SCN neuron
- Based on interlocked feedback loops
- Light activates *per/cry* expression
- Cells are coupled (and synchronized) by neurotransmitters

Mammalian circadian clock

Central clock (pacemaker): SCN





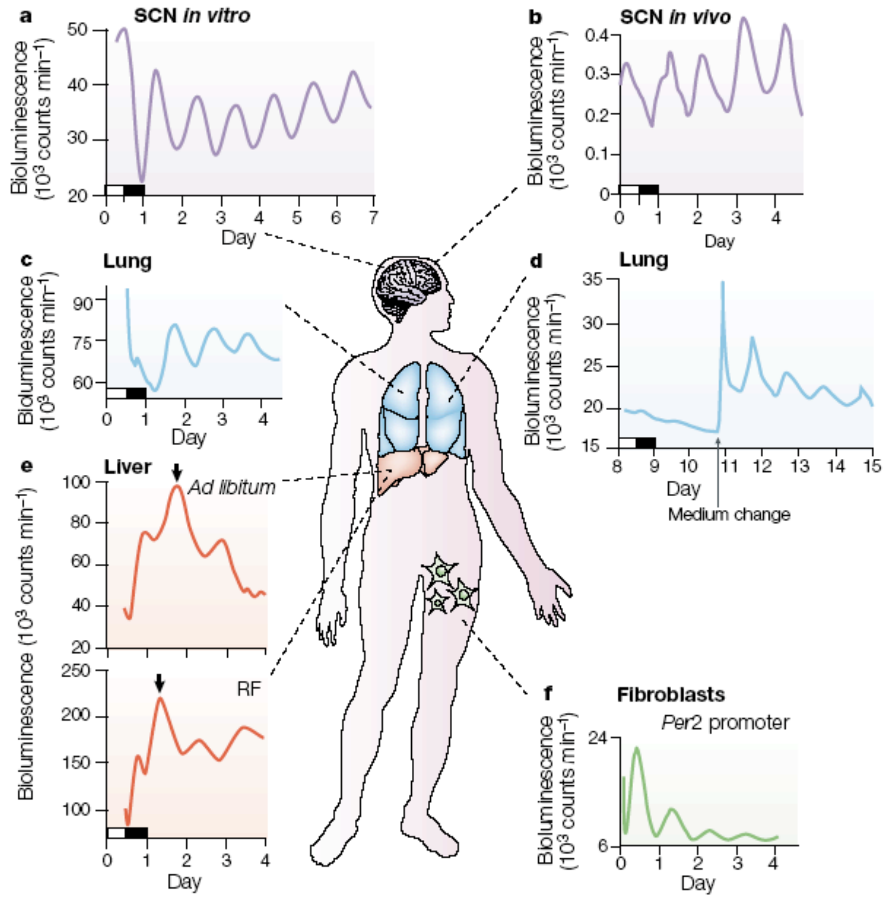
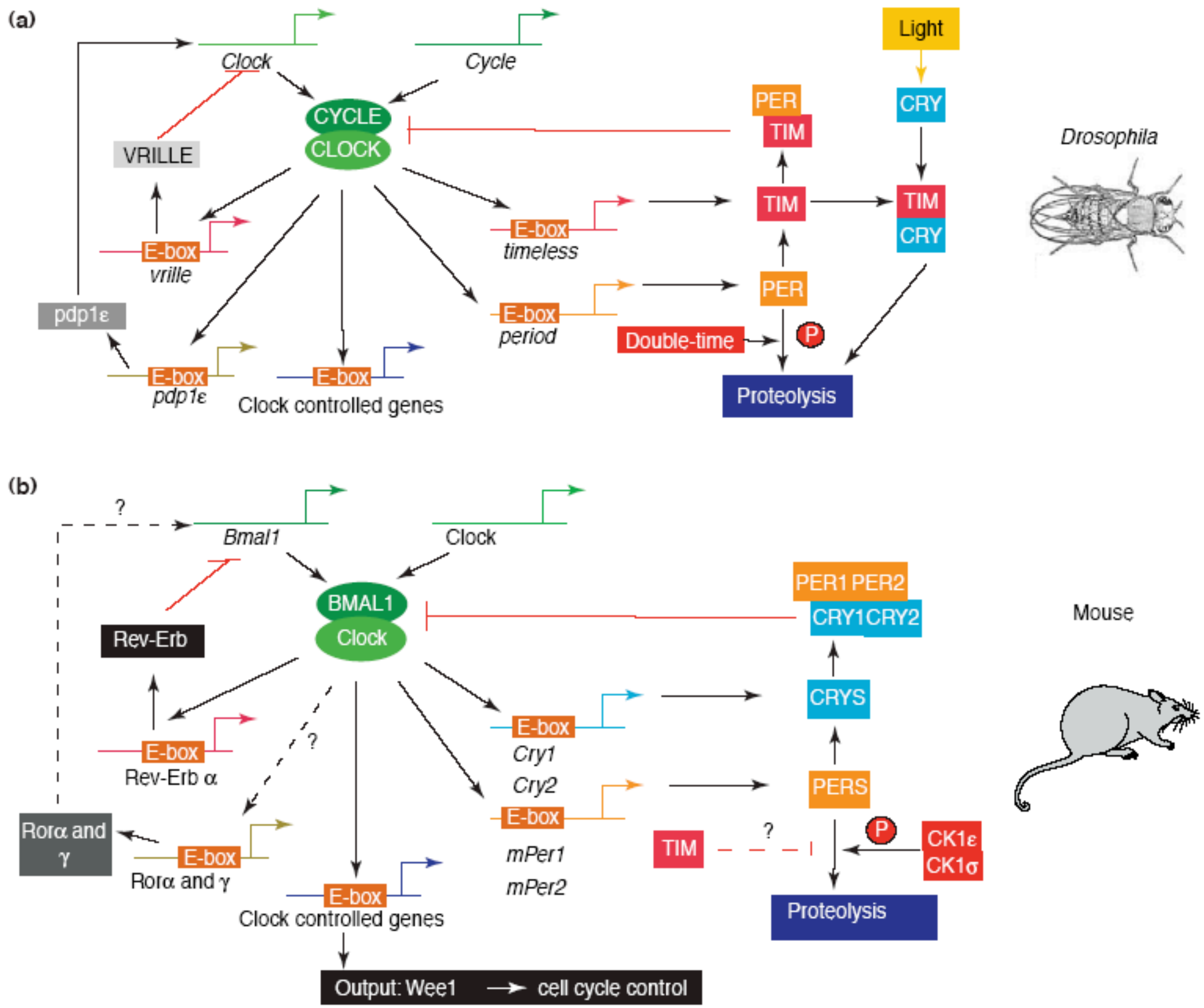


Figure 3 | *Per::luciferase* **transgenes reveal a diversity of tissue-based circadian oscillators.**

Molecular mechanism of the circadian clock

Hastings (2003) *Nat Rev Neurosci 4*: 649-61.

Mammalian circadian clock



Mammalian circadian clock

Circadian oscillation of BMAL1, a partner of a mammalian clock gene Clock, in rat suprachiasmatic nucleus.
Honma S, Ikeda M, Abe H, Tanahashi Y, Namihira M, Honma K, Nomura M. *Biochem Biophys Res Commun* (1998) 250:83-7.

Three period homologs in mammals: differential light responses in the suprachiasmatic circadian clock and oscillating transcripts outside of brain.
Takumi T, Taguchi K, Miyake S, Sakakida Y, Takashima N, Matsubara C, Maebayashi Y, Okumura K, Takekida S, Yamamoto S, Yagita K, Yan L, Young MW, Okamura H. *Neuron* (1998) 20:1103-10.

A new mammalian period gene predominantly expressed in the suprachiasmatic nucleus.
Takumi T, Matsubara C, Shigeyoshi Y, Taguchi K, Yagita K, Maebayashi Y, Sakakida Y, Okumura K, Takashima N, Okamura H. *Genes Cells* (1998) 3:167-76.

A differential response of two putative mammalian circadian regulators, mper1 and mper2, to light.
Albrecht U, Sun ZS, Eichele G, Lee CC. *Cell* (1997) 91:1055-64.

Light-induced resetting of a mammalian circadian clock is associated with rapid induction of the mPer1 transcript.
Shigeyoshi Y, Taguchi K, Yamamoto S, Takekida S, Yan L, Tei H, Moriya T, Shibata S, Loros JJ, Dunlap JC, Okamura H. *Cell* (1997) 91:1043-53.

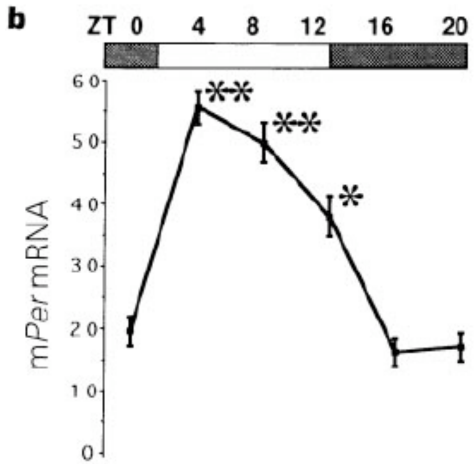
Mammalian circadian autoregulatory loop: a timeless ortholog and mPer1 interact and negatively regulate CLOCK-BMAL1-induced transcription.
Sangoram AM, Saez L, Antoch MP, Gekakis N, Staknis D, Whiteley A, Fruechte EM, Vitaterna MH, Shimomura K, King DP, Young MW, Weitz CJ, Takahashi JS. *Neuron* (1998) 21:1101-13.

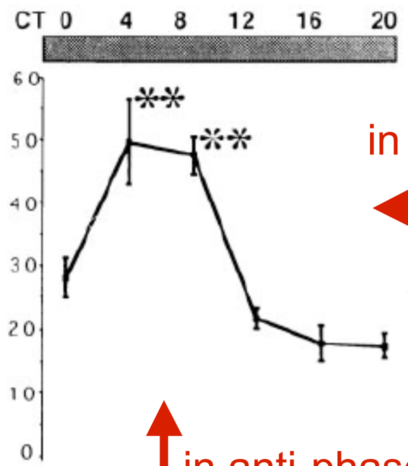
Role of mouse cryptochrome blue-light photoreceptor in circadian photoresponses.
Thresher RJ, Vitaterna MH, Miyamoto Y, Kazantsev A, Hsu DS, Petit C, Selby CP, Dawut L, Smithies O, Takahashi JS, Sancar A. *Science* (1998) 282:1490-4

Mammalian circadian clock

Circadian oscillation of *mper1, cry1* and Bmal1 in mouse

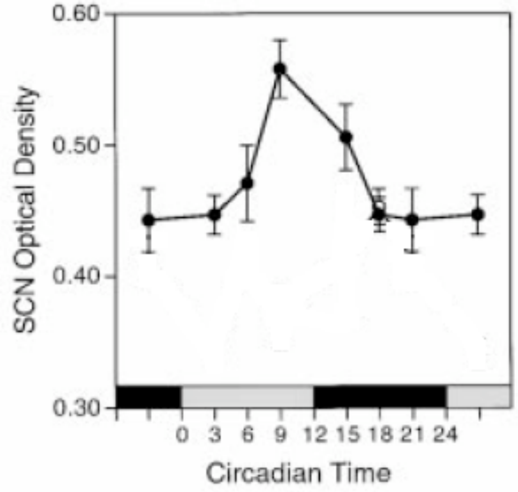
mper1





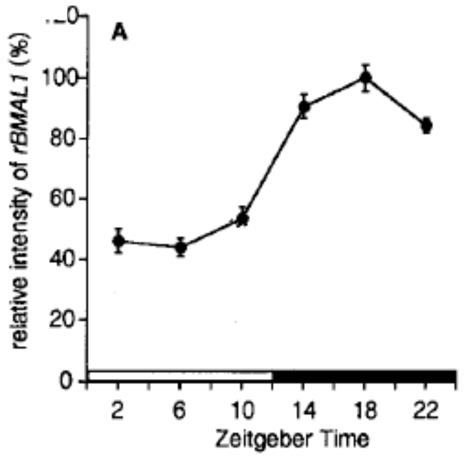
in phase

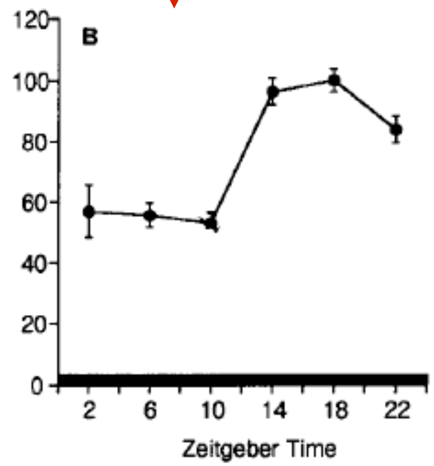
cry1



in anti-phase

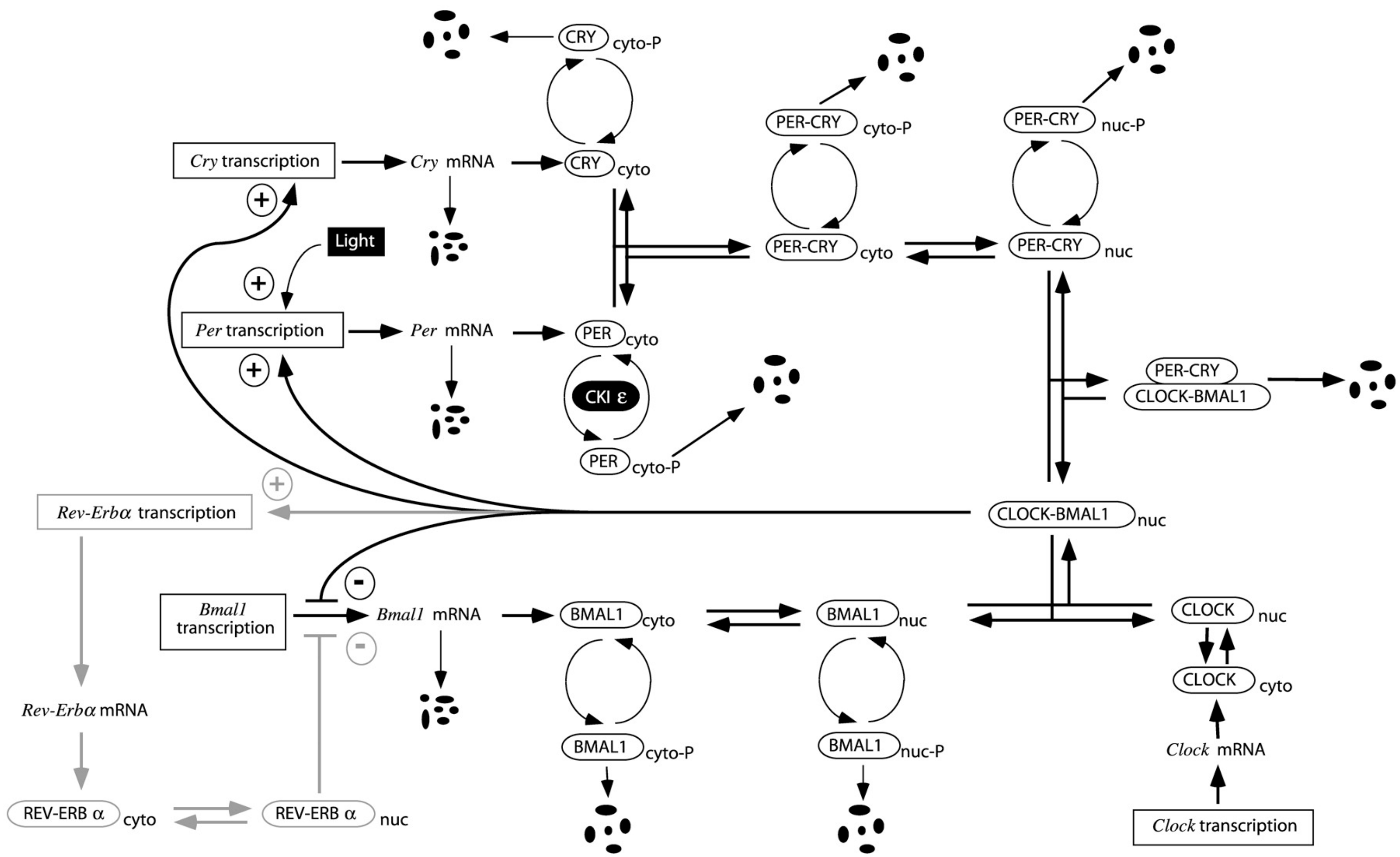
bmal1





- Tei *et al* (1997) Circadian oscillation of a mammalian homologue of the *Drosophila* period gene. *Nature*. 389:512-6
- Honma *et al* (1998) Circadian oscillation of BMAL1, a partner of a mammalian clock gene Clock, in rat suprachiasmatic nucleus. Biochem Biophys Res Commun. 250:83-7.
- Kume *et al* (1999) mCRY1 and mCRY2 are essential components of the negative limb of the circadian clock feedback loop. Cell 98:193-205.

Mammalian circadian clock

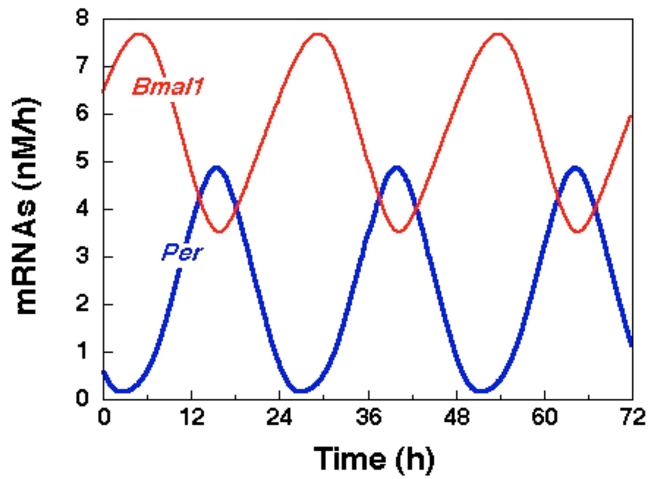


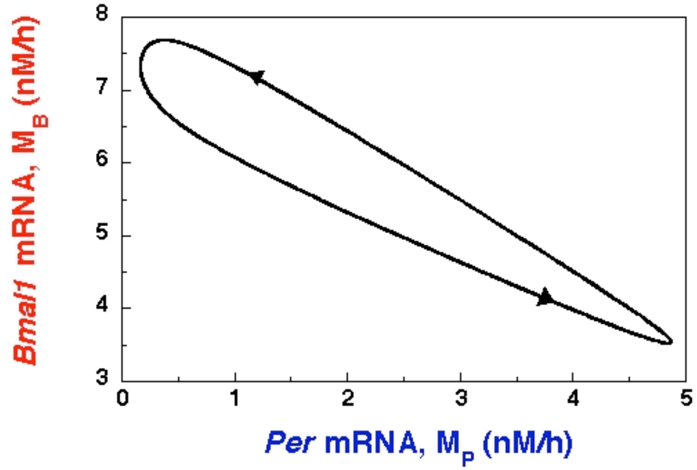
16-variable model including
per, cry, bmal1, rev-erbα

Leloup J-C & Goldbeter A (2003) Toward a detailed computational model for the mammalian circadian clock. *Proc Natl Acad Sci USA.* 100: 7051-7056.

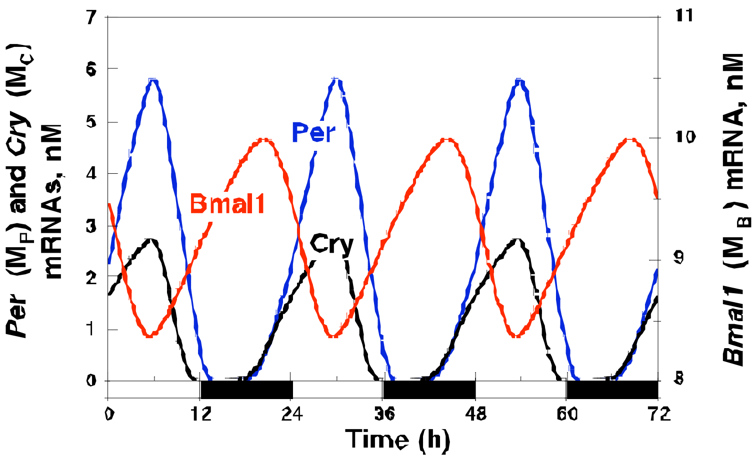
Mammalian circadian clock

Limit-cycle oscillations (in constant conditions, DD)

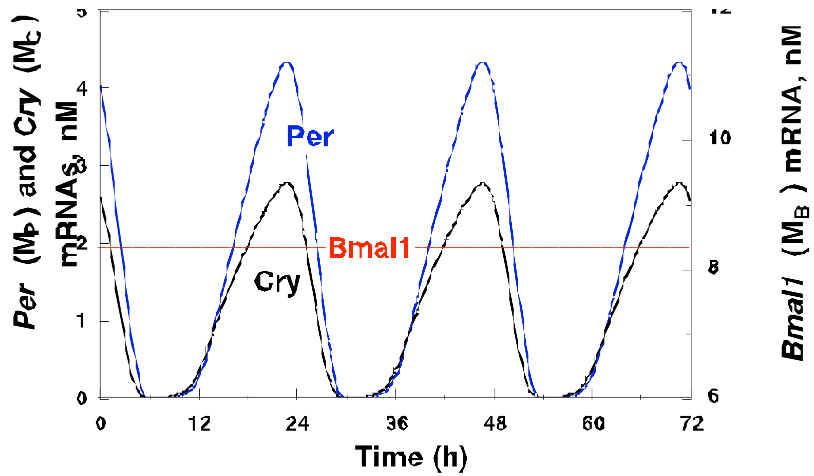




Oscillations in LD conditions



Oscillations of Per/Cry with Bmal1 mRNA maintained constant



Mammalian circadian clock

Physiological properties studied with the model:

Sleep phase disorders

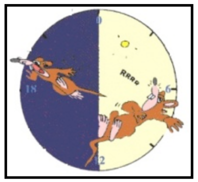
The model can be used to understand the links between the mutation of clock genes and their impact on the period and entrainment phase of the circadian oscillator.

Jet lag and chronic jet lag

The model can be used to predict the resynchronization time after jet lags (i.e. shift in the LD cycle). The effect of pre-jet-lag treatment (e.g. by the light) can also be simulated.

Shift work

The model can be used to assess the impact of various shift work timings on the circadian clocks.



Link with cell cycle and cancer (chronotherapy)

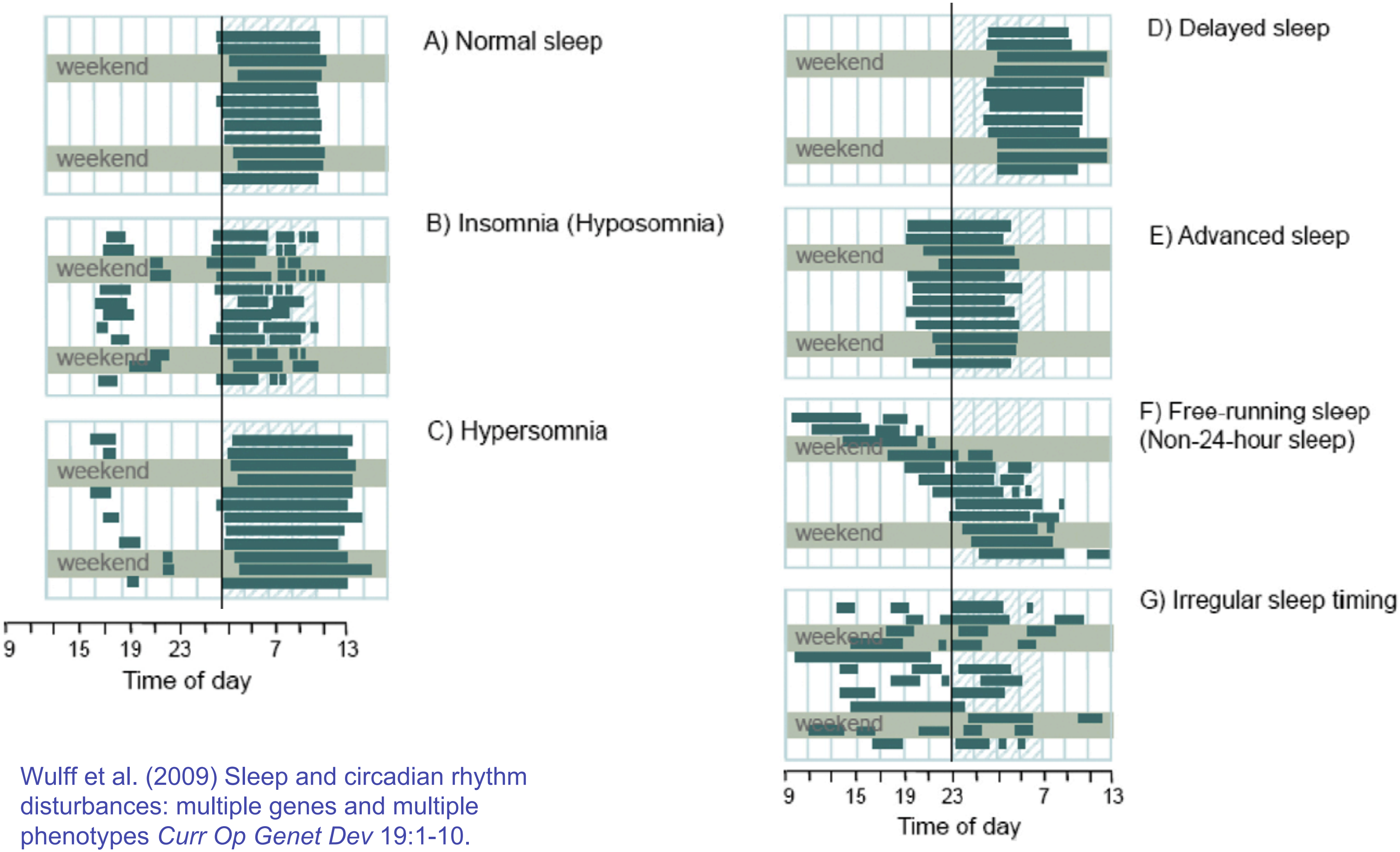
The model, in combination with a model for the cell cycle, can be used to assess the effect of anti-cancer drugs (and of their administration profiles) on the cell cycle.

Sleep phase disorders

Sleep-wake disorders

Sleep phase disorders

Different types of sleep phase syndromes



Wulff et al. (2009) Sleep and circadian rhythm disturbances: multiple genes and multiple phenotypes *Curr Op Genet Dev* 19:1-10.

Sleep phase disorders

An *hPer2* phosphorylation site mutation in familial advanced sleep-phase syndrome (FASPS).

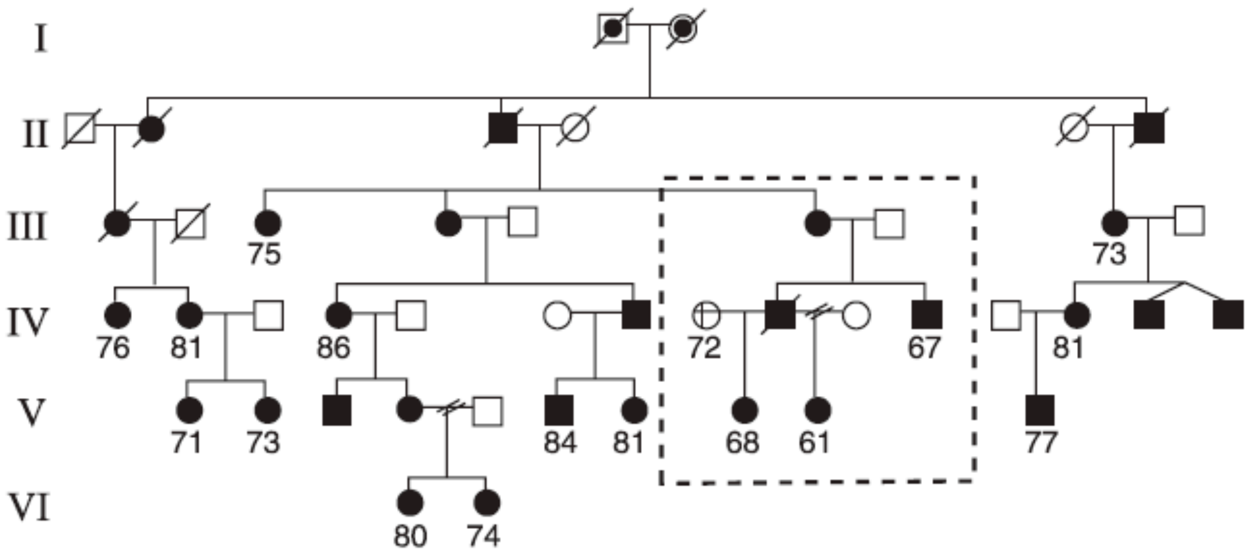
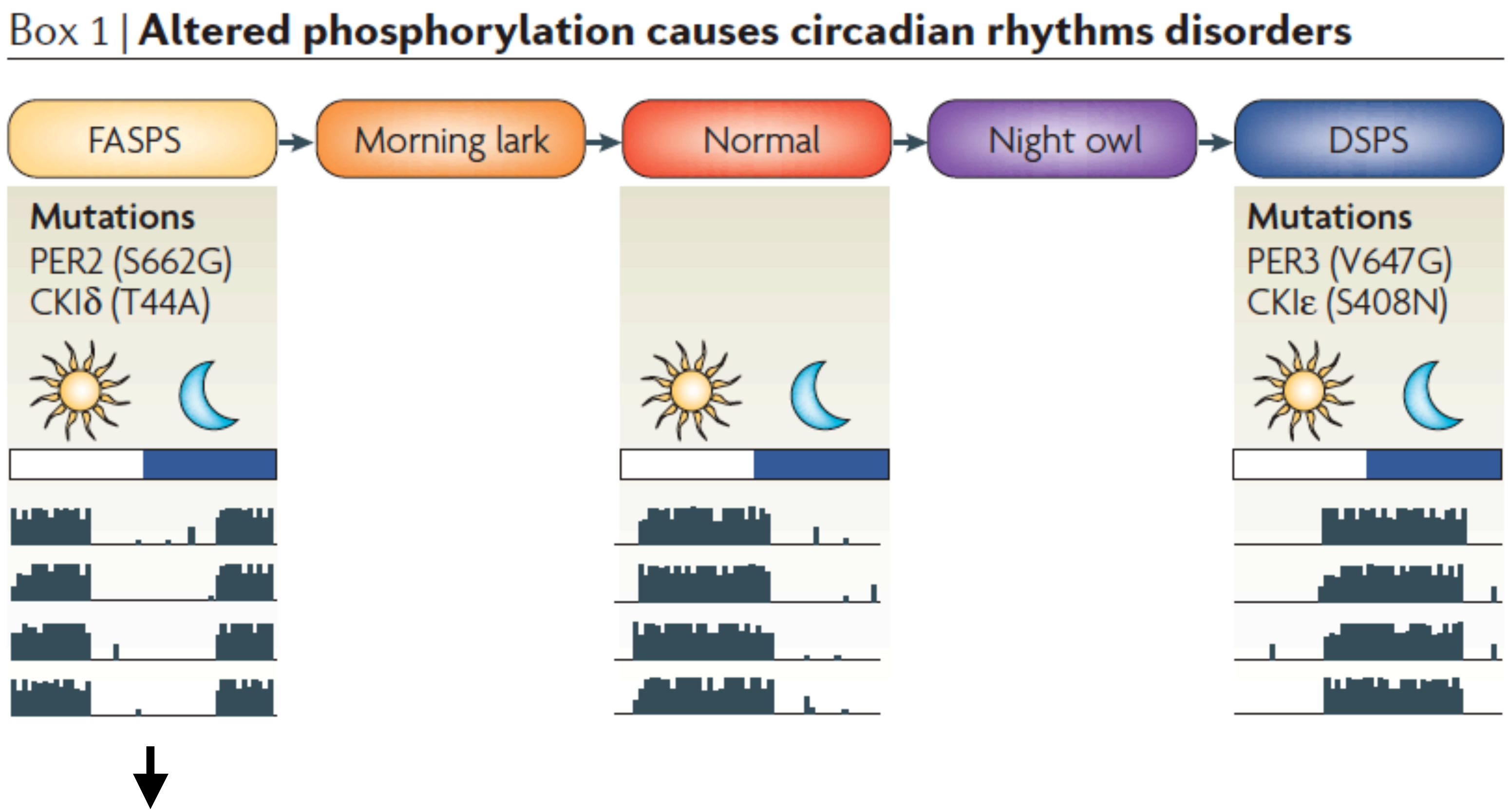


Fig. 1. ASPS kindred 2174. Horne-Östberg scores are shown below individuals. The dotted line marks a branch (branch 3) where the ASPS phenotype does not cosegregate with the mutation. Circles, women; squares, men; filled circles and squares, affected individuals; empty circles and squares, unaffected individuals. Unknown individuals (not meeting strict criteria for being "affected" or "unaffected") were eliminated from this pedigree for the sake of simplicity.

Toh KL *et al.* (2001) *Science* 291:1040-3.

Sleep phase disorders

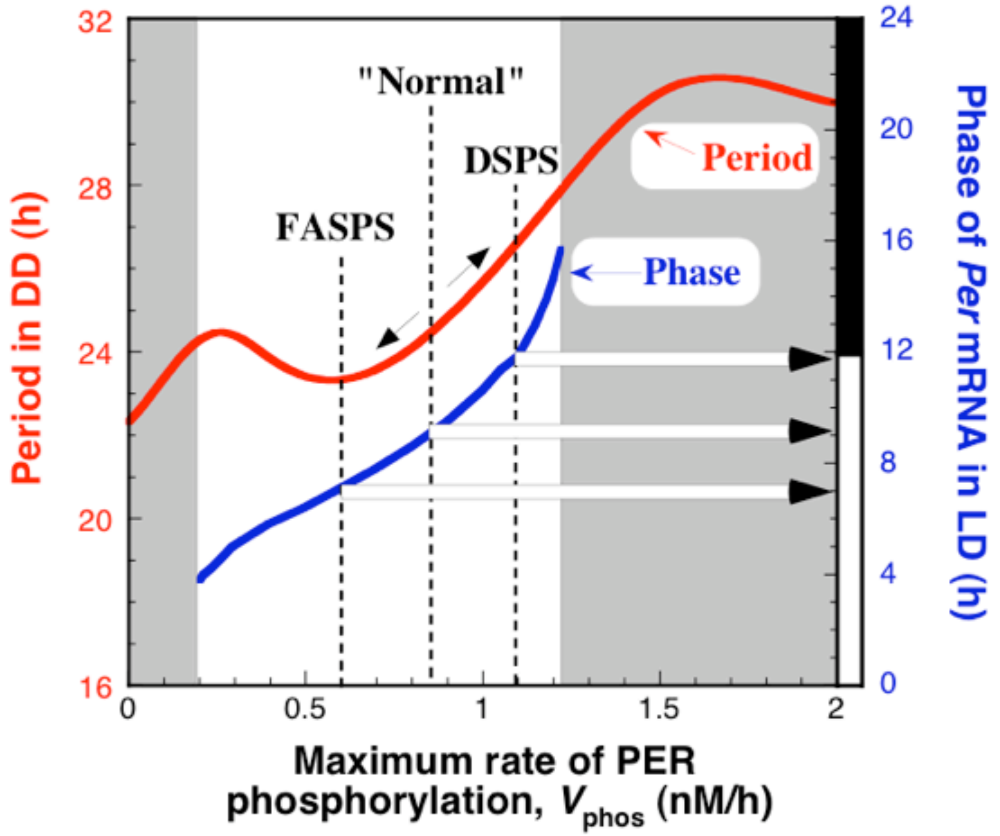


- FASPS patients have a mutation within the casein kinase ε (CKIε) binding region of PER2, which causes hypophosphorylation of PER2.
- A mutation in the human CKIδ gene was found in a family with FASPS, leading to a decrease of the enzymatic activity of the kinase.

Gallego & Virshup (2007) *Nature Reviews Mol Cell Biol* **8**:139-148

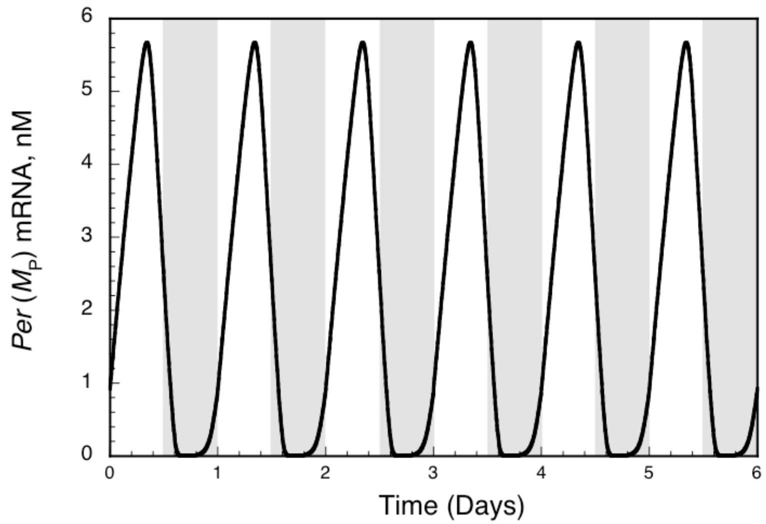
Sleep phase disorders

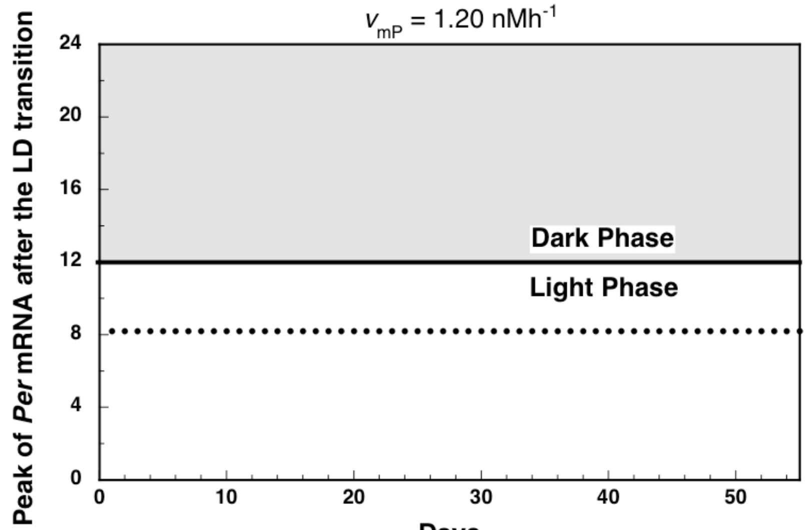
An *hPer2* phosphorylation site mutation in familial advanced sleep-phase syndrome (FASPS).



Sleep phase disorders

"Normal" Case: entrainment and phase locking





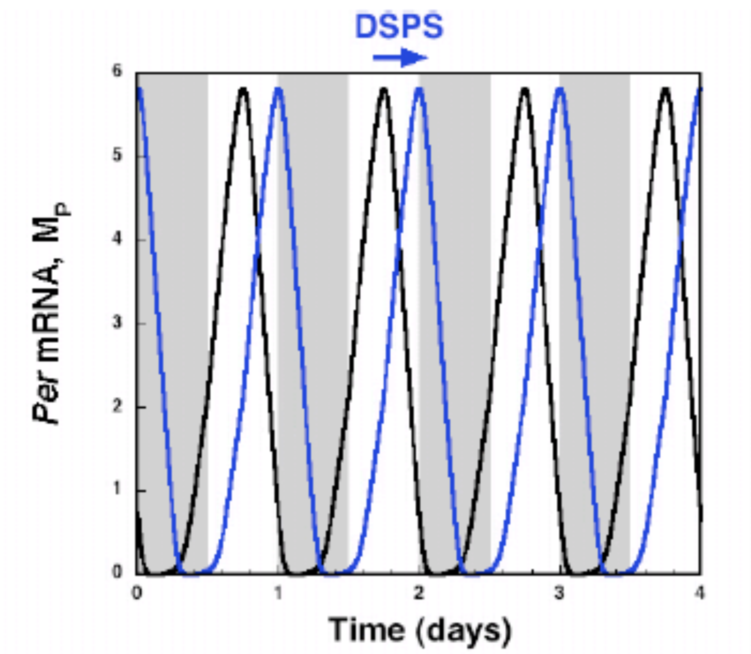
In normal conditions, under the periodic forcing by the light-dark cycle (LD) the circadian rhythm is **entrained** and the phase of the oscillations (with respect to the LD cycle) is **locked** (i.e. constant).

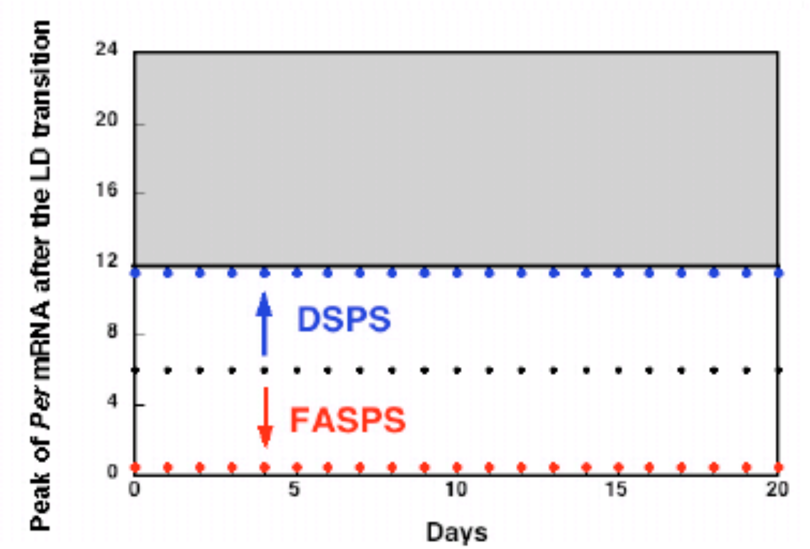
As a function of the conditions (parameters values, strength of the forcing), several pathological cases can be observed:

- Non 24h Sleep Phase Syndrom (SPS)
- Non 24h SPS with jump
- Irregular SPS

Sleep phase disorders

FASPS & DSPS

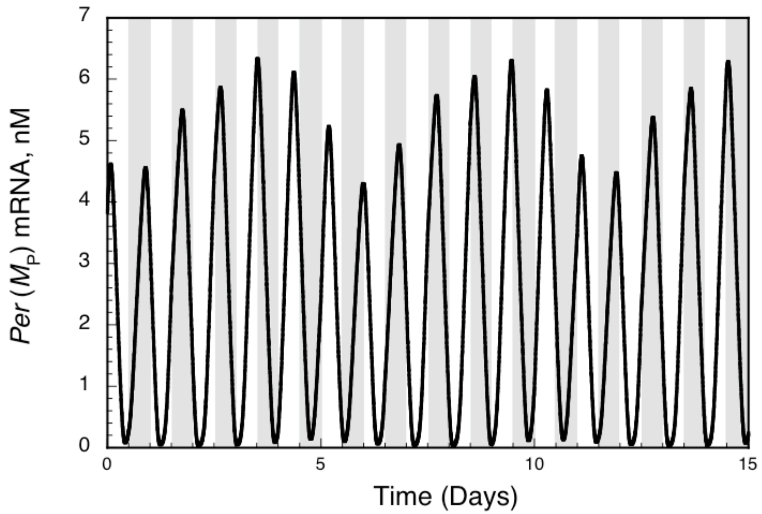


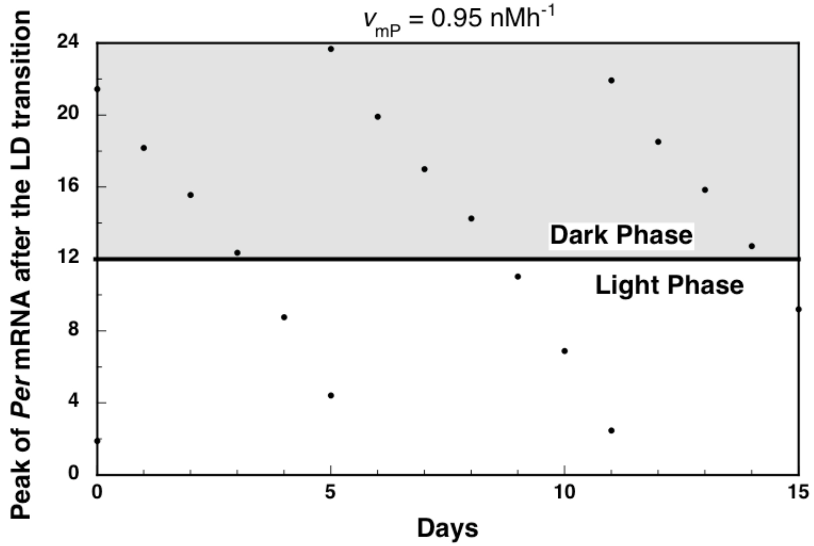


FASPS & DSPS are characterized by a "proper" entrainment (in the sense that the phase is locked), but with a shift in the phase of the oscillations with respect to the LD cycle.

Sleep phase disorders

Non-24h Sleep Phase Syndrom



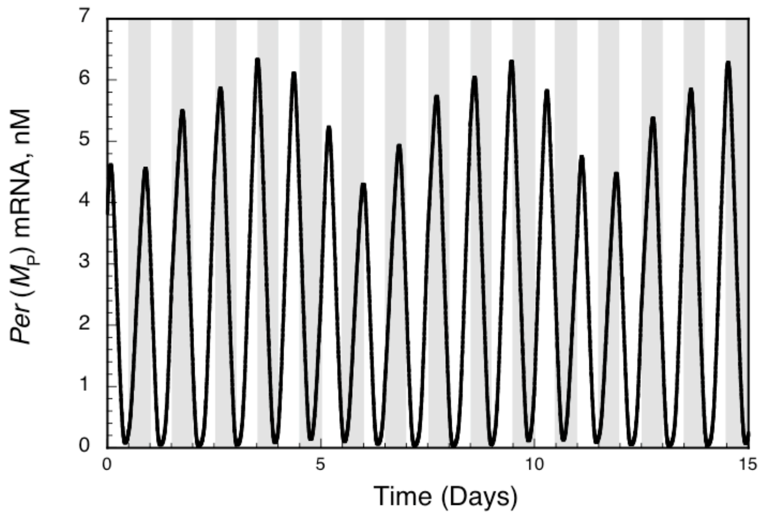


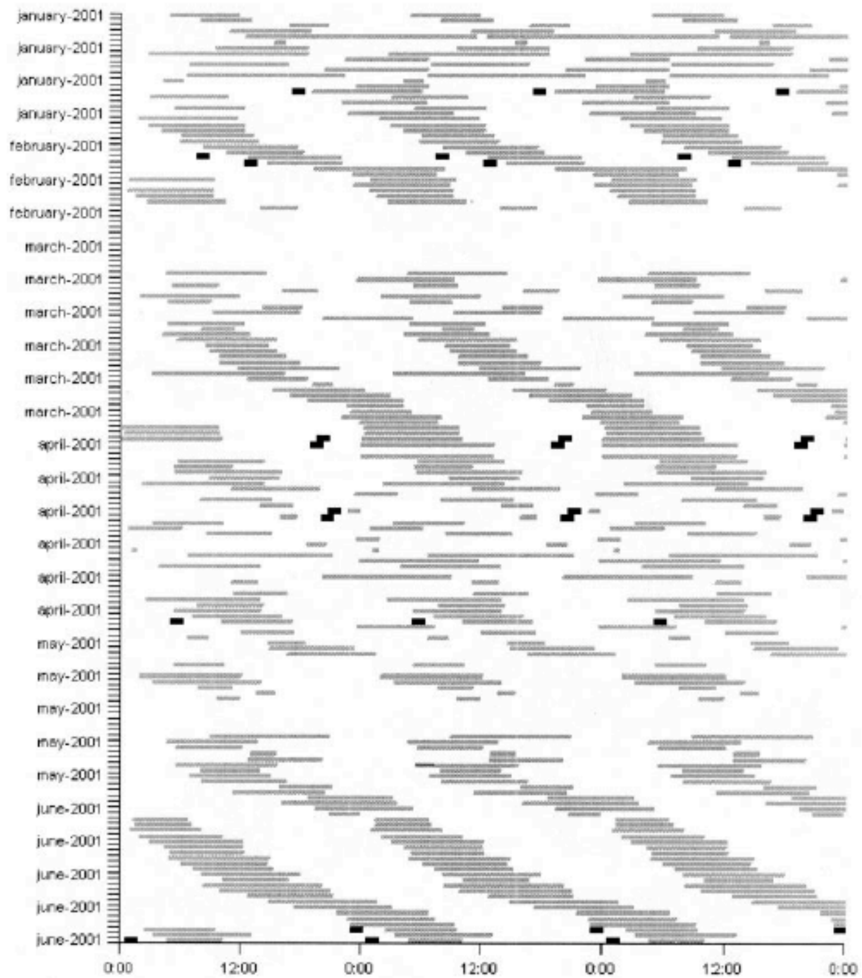
In some conditions, the oscillations are not entrained by the light-dark cycle. In this case, we may observe a **quasi-periodic behavior**: the oscillations are relatively regular, but there are some beats in their amplitude and their phase is not locked (i.e. the period is not precisely 24h). As a consequence, the rhythm (and thus the sleeping phase) is shifted more and more every day. This so-called **non-24h syndrom** was reported in blind patients, but also, rarely, in sighted patients.

NB: this syndrome is sometimes also called **free-running syndrom.** It should be noted that from the theoretical point of view the 2 types of dynamics are different (beats is a consequence of the periodic forcing and would not appear in free-run).

Sleep phase disorders

Non-24h Sleep Phase Syndrom





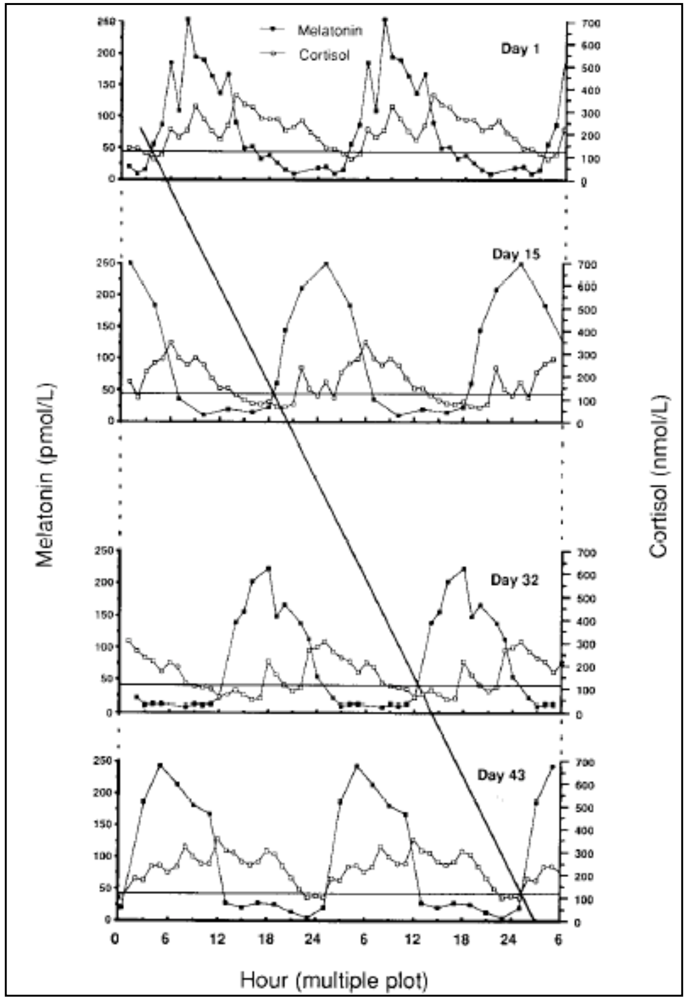
The authors report the case of a 39-year-old sighted woman who displayed non-24-hour sleep–wake cycles following a car accident.

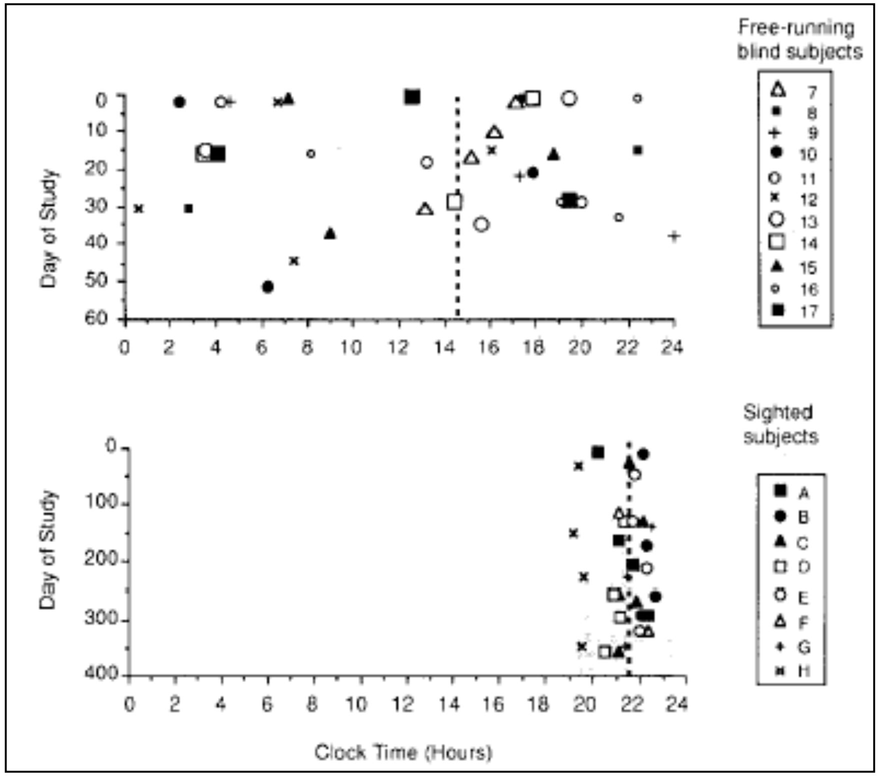
Boivin *et al.* (1992) Non-24-hour sleep-wake syndrome following a car accident. *Neurology* 60:1841-3.

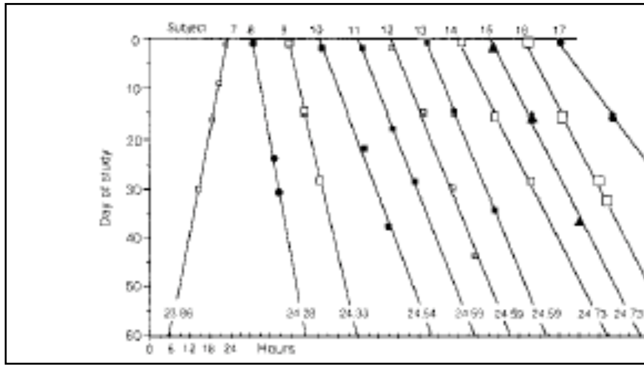
Sleep phase disorders

Non-24h SPS

(free running syndrom?)



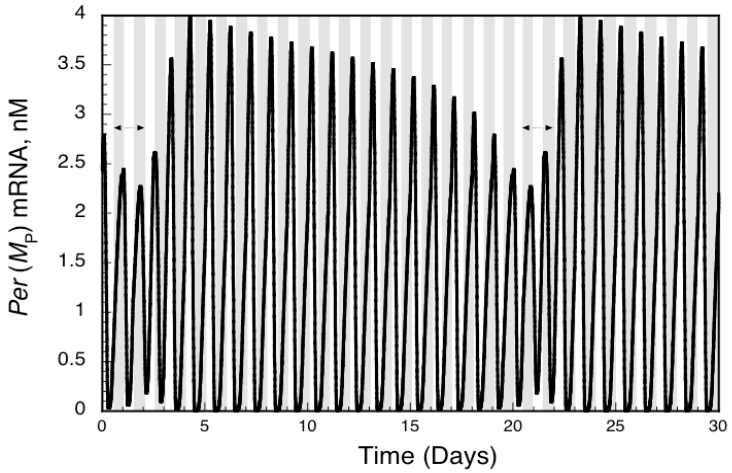


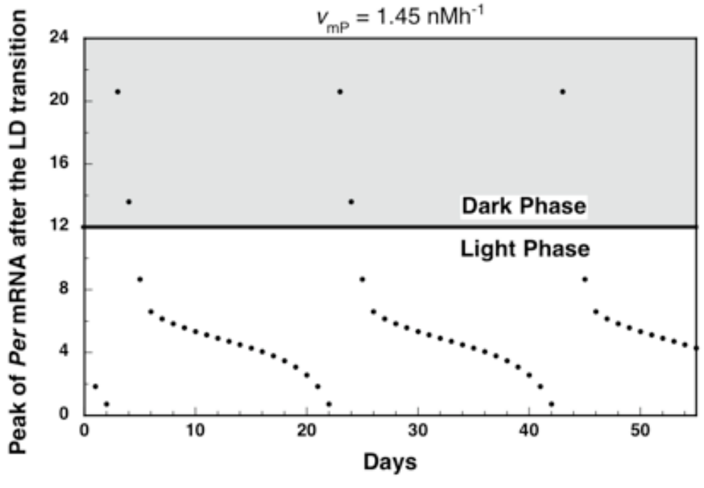


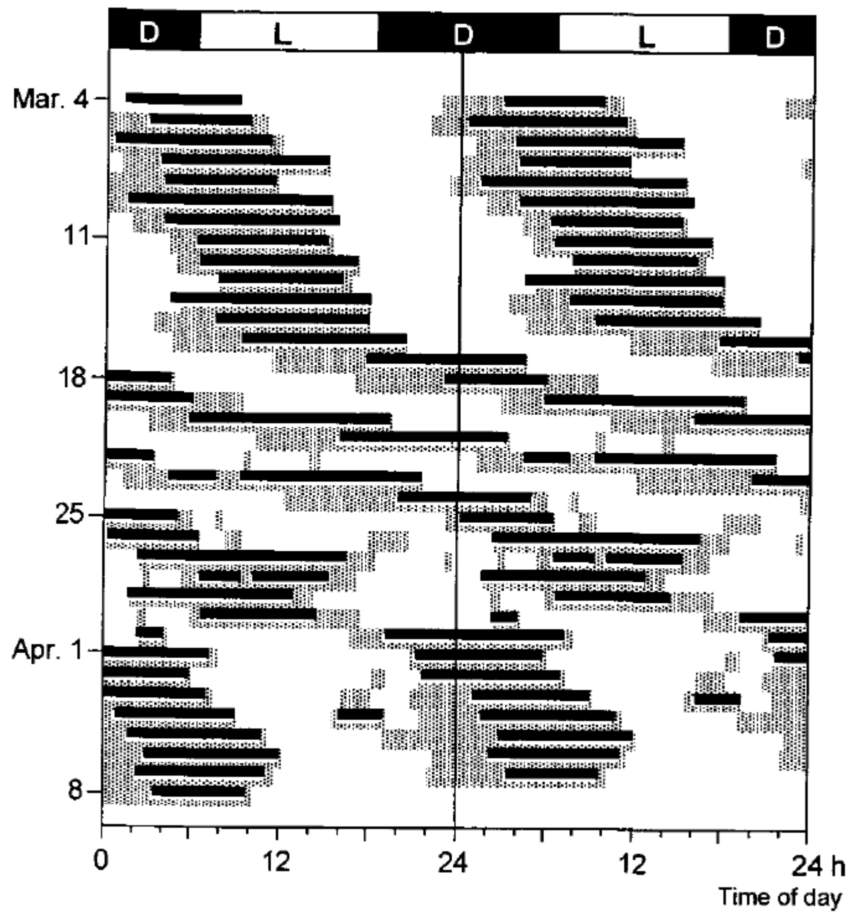
Sack RL *et al.* (1992) Circadian rhythm abnormalities in totally blind people. *J Clin Endocrinol Metab* 75:127-34.

Sleep phase disorders

Non-24 h SPS (with phase jumps)



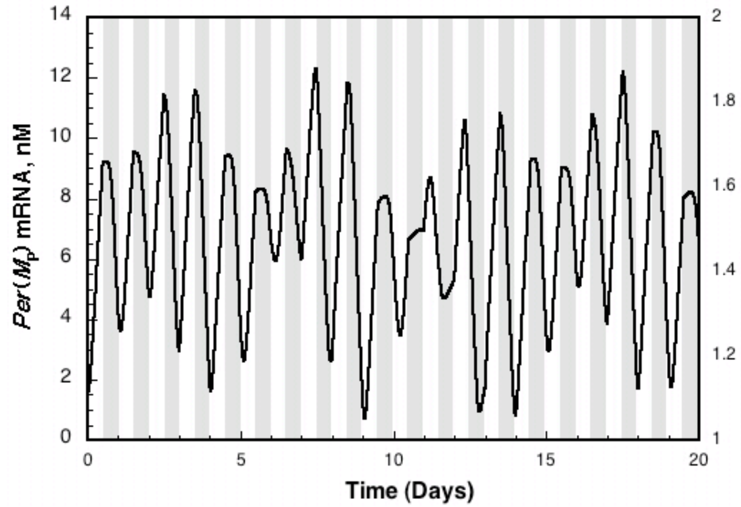


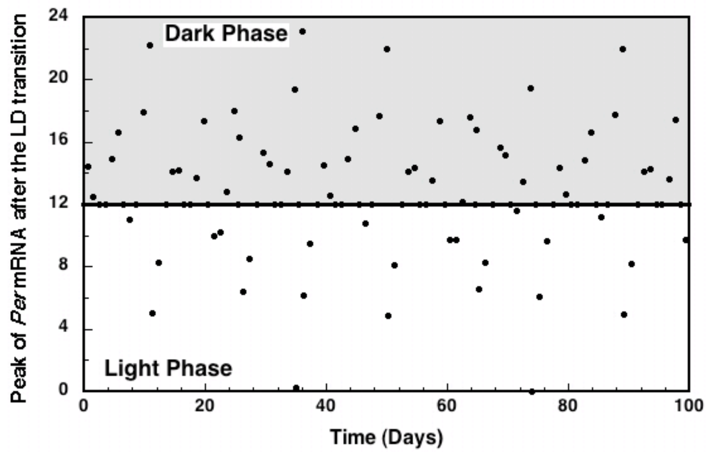


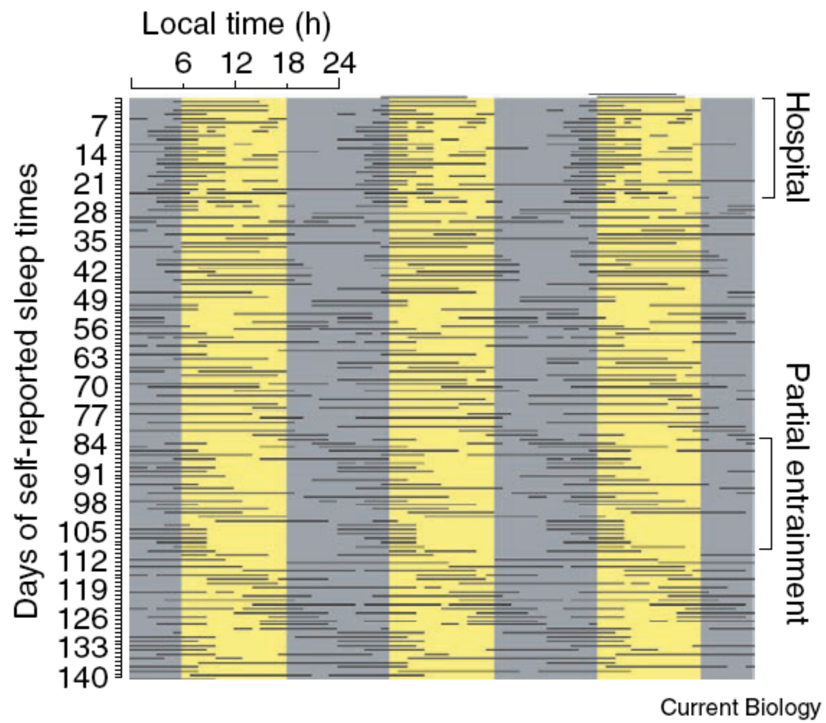
Uchiyama *et al.* (1996) *Sleep* 19:637-40.

Sleep phase disorders

Irregular Sleep Phase Syndrom





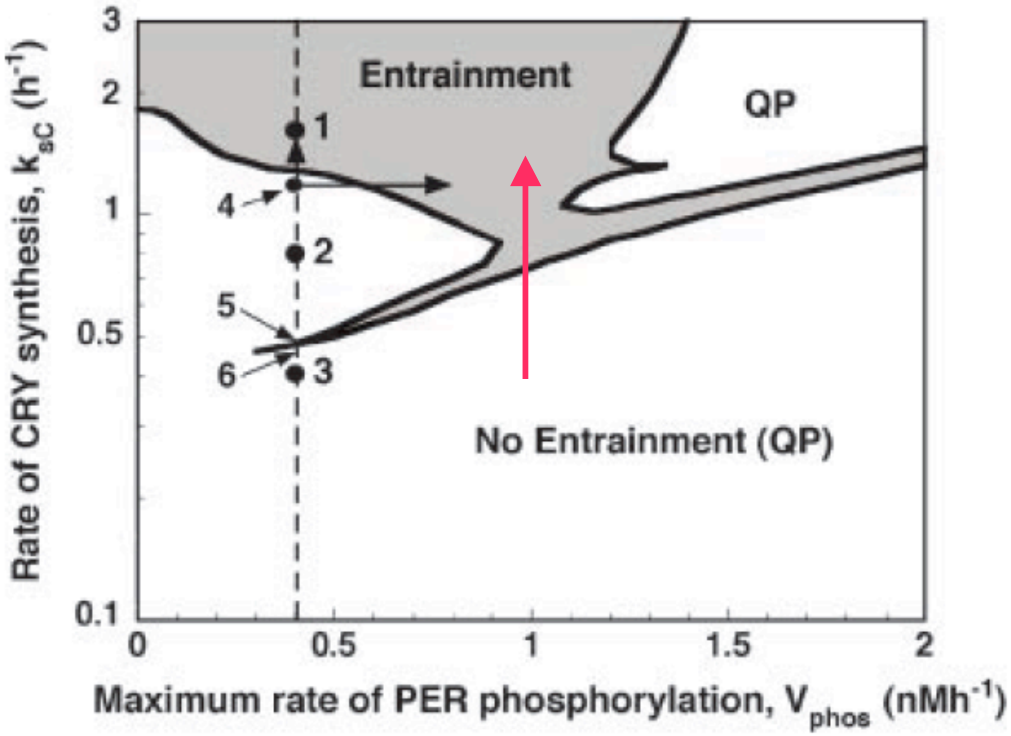


Roenneberg & Merrow (2003)
Curr Biol 13:R198-R207.

Sleep phase disorders

How to restore circadian entrainment?

The model can be used to identify the disregulation responsible for the lack of entrainment and to suggest ways to restore a proper entrainment.



The lack of entrainment in the model was shown to be due to a inappropriate balance between PER and CRY levels.

Thus, by tuning parameters such as the CRY synthesis rate (or PER degradation rate), it is possible to restore entrainment (see red arrow).

Leloup JC, Goldbeter A (2008) *Bioessays* 30:590-600.

Sleep phase disorders

How to restore circadian entrainment?

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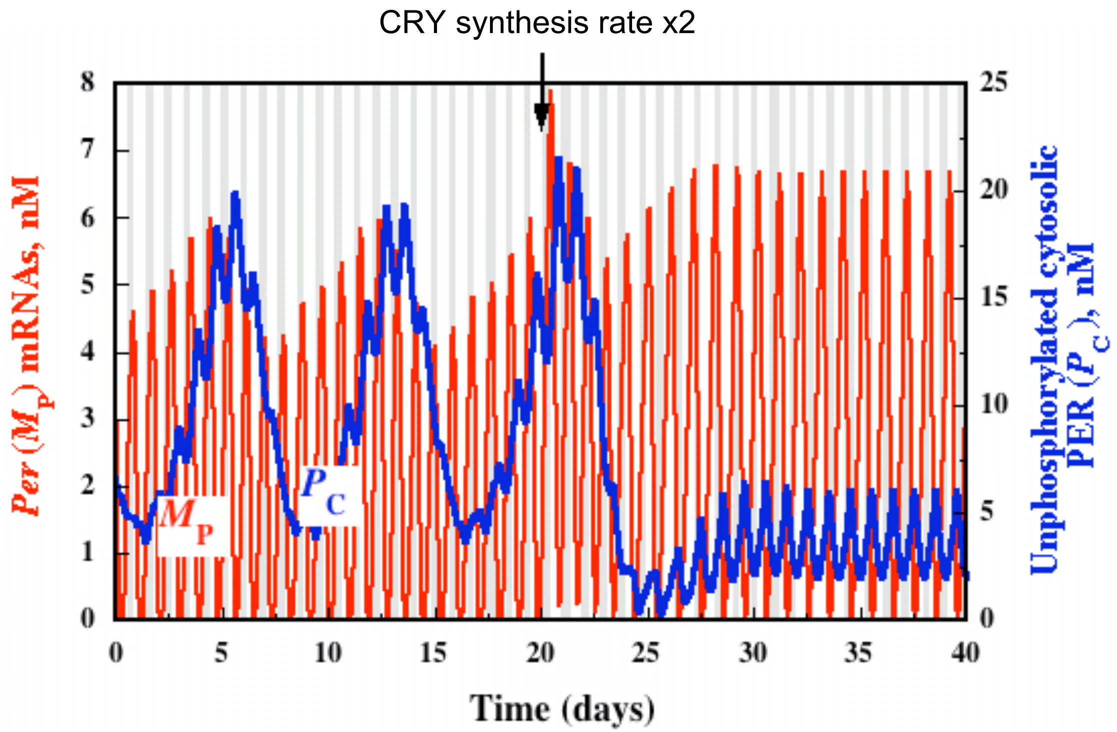


Recovery of a proper entrainment by increasing (doubling) the CRY synthesis rate.

Leloup JC, Goldbeter A (2008) *Bioessays* 30:590-600.

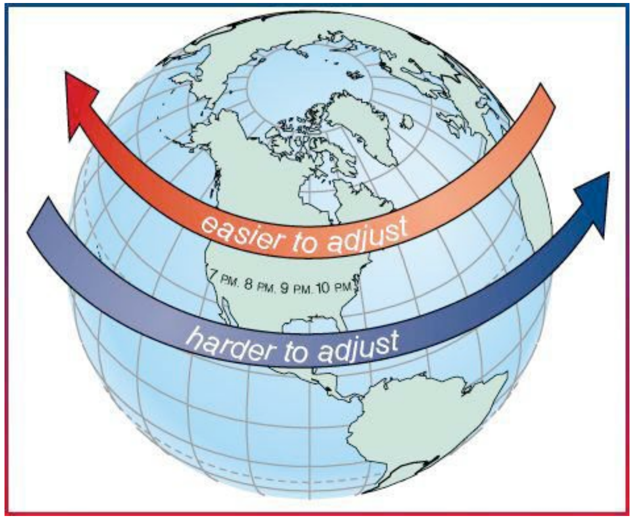
Jet lag

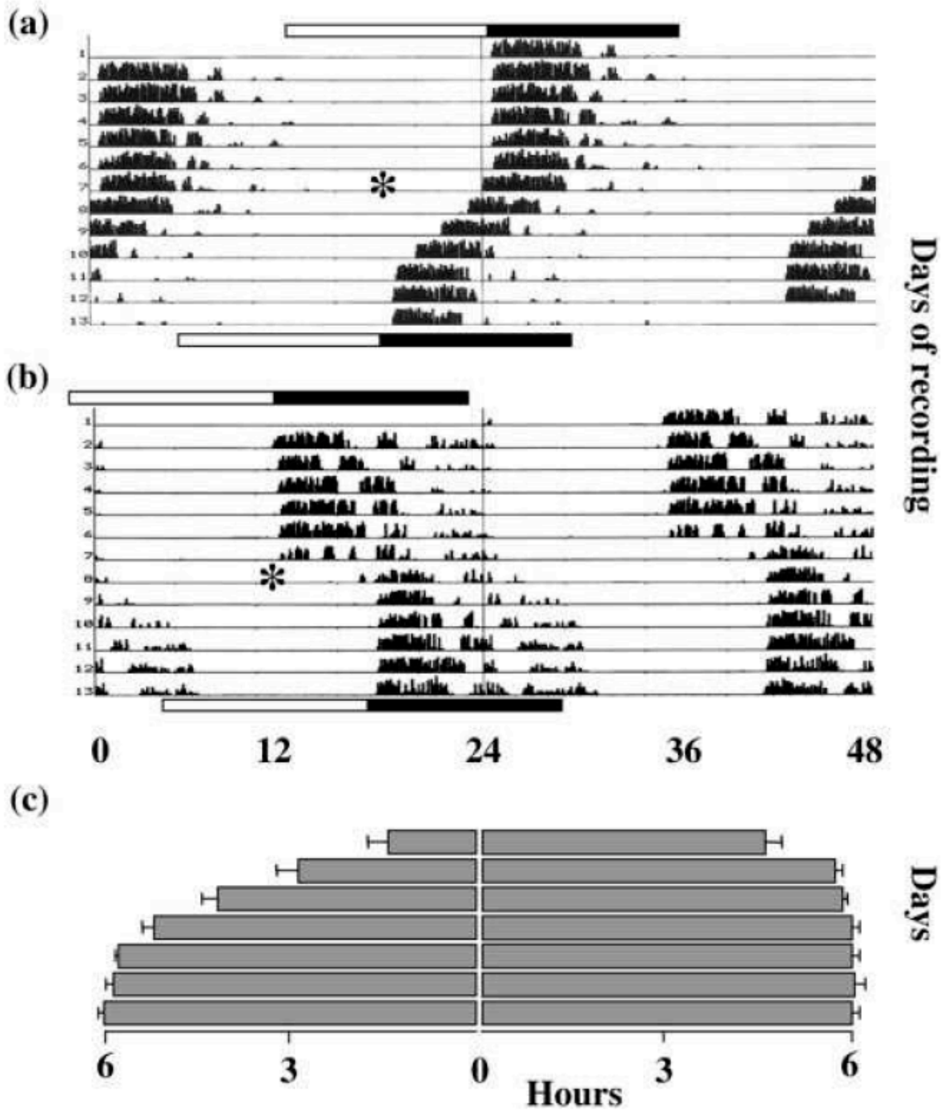
Jet lag

Jet lag

Resynchronization after a jet lag

Differential resynchronization of circadian clock gene expression within the suprachiasmatic nuclei of mice subjected to a jet lag.





Reddy AB *et al.* (2002) *J Neurosci* 22:7326-30.

Jet lag

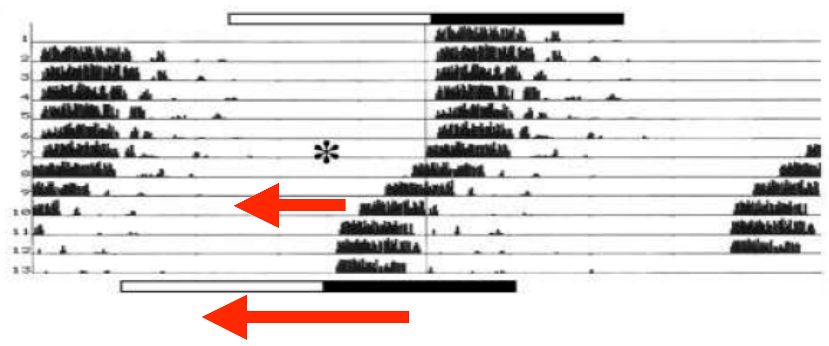
Orthodromic vs antidromic adjustment

Orthodromic re-entrainment occurs when circadian rhythms re-entrain by phase shifting in the **same direction** to the shift in external time.

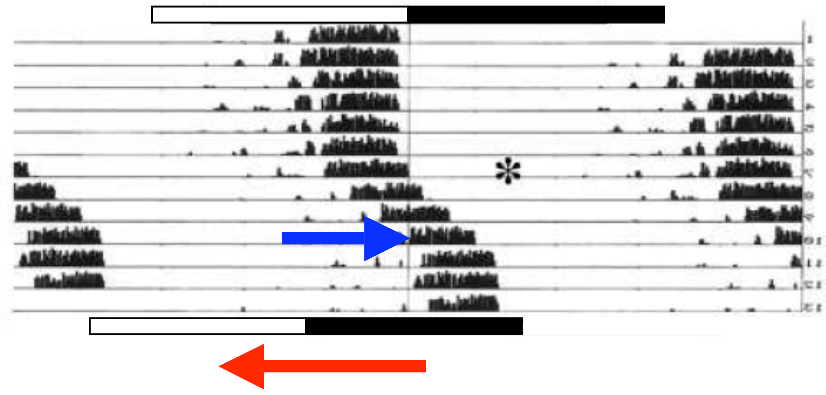
Antidromic re-entrainment occurs when circadian rhythms re-entrain by phase shifting in the **opposite direction** to the shift in external time, such as a phase delay instead of a phase advance after eastward travel.

(Burgess *et al*., 2003, *J Biol Rhythms* 18:318-28)

Orthodromic adjustment



Antidromic adjustment



Antidromic shifts are quite common :

- **1 of 7 people** following an 8-h eastward flight.
  (Arendt *et al*., 1987, *Ergonomics* 30:1379-93)

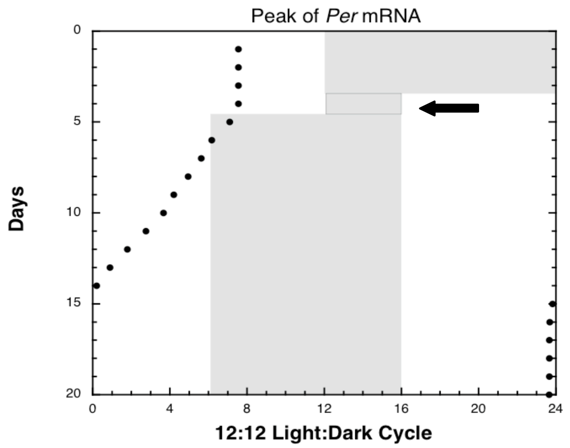
- **4 of 8 people** following a 9-h eastward flight.
  (Klein *et al*., 1977, RR Mackie ed, 111-31, Plenum, NY)

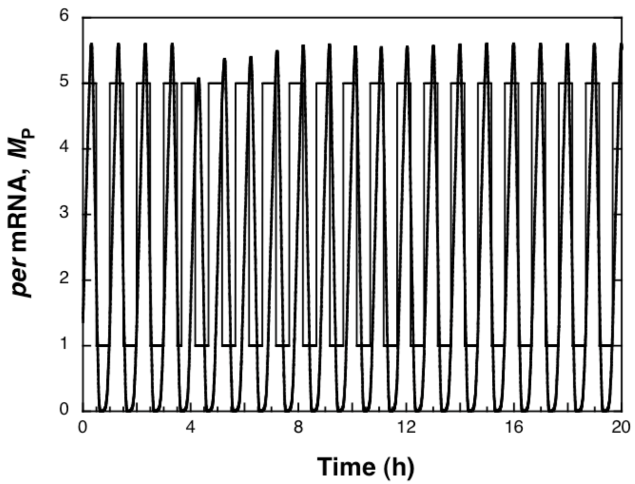
Source: JC Leloup

Jet lag

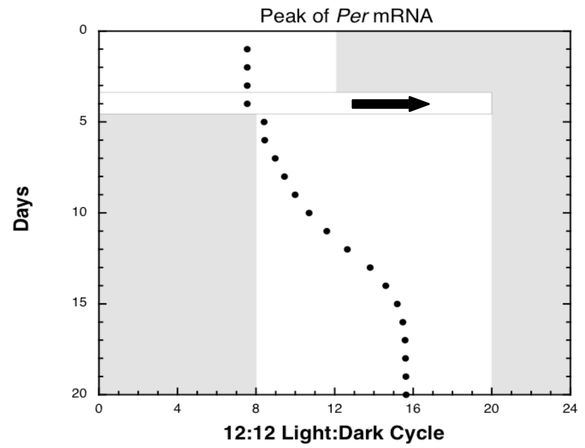
Orthodromic vs antidromic adjustment

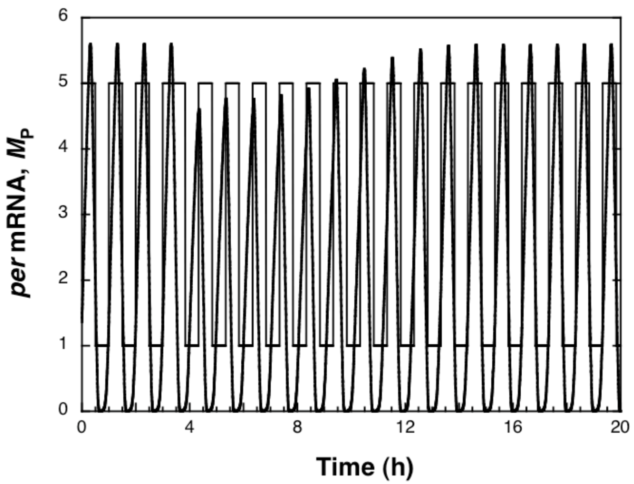
Phase Advance





Phase Delay

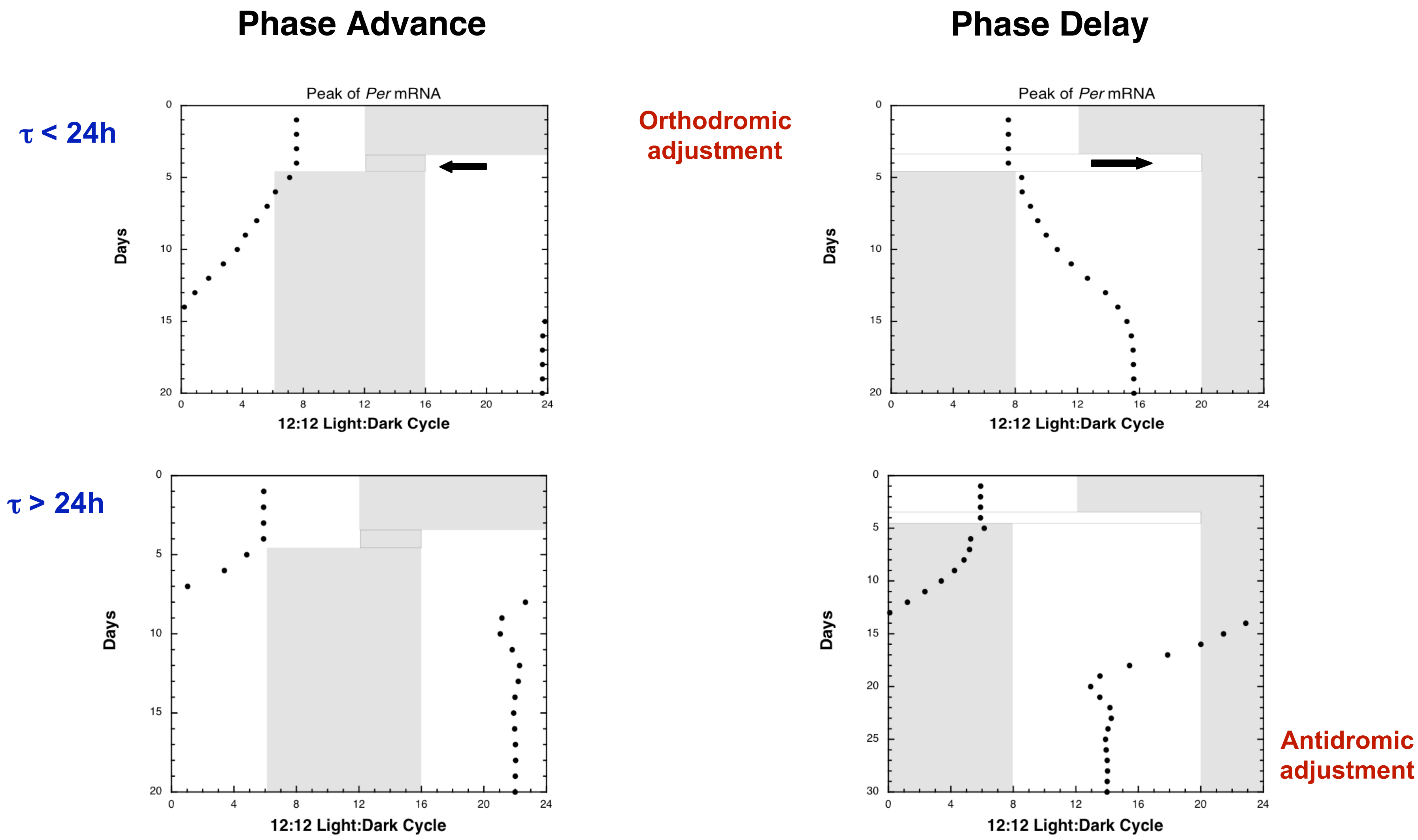




Orthodromic adjustment

Jet lag

Orthodromic vs antidromic adjustment



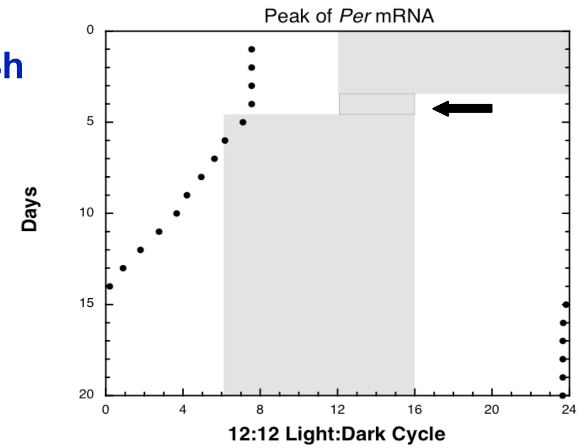
Jet lag

Orthodromic vs antidromic adjustment

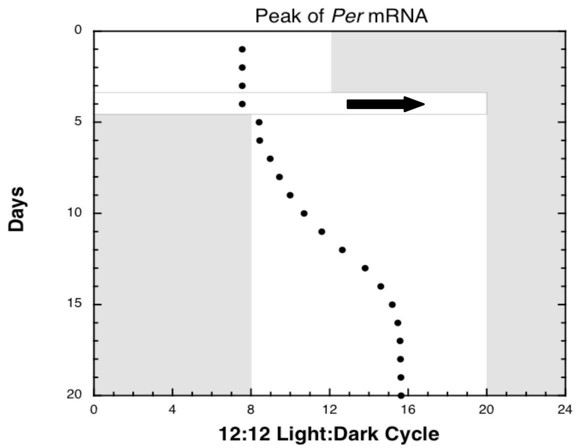
Phase Advance

Phase Delay

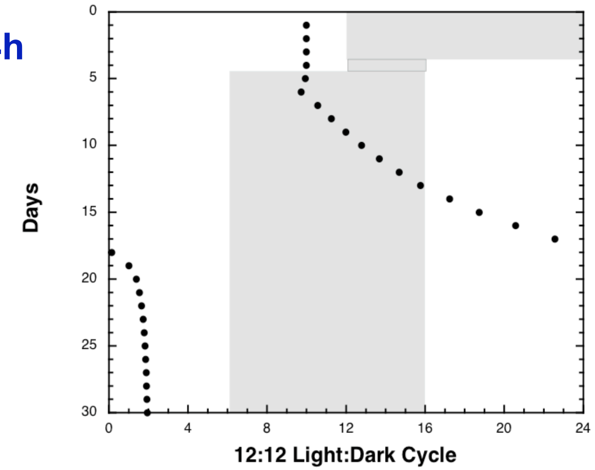
τ < 24h



Orthodromic adjustment

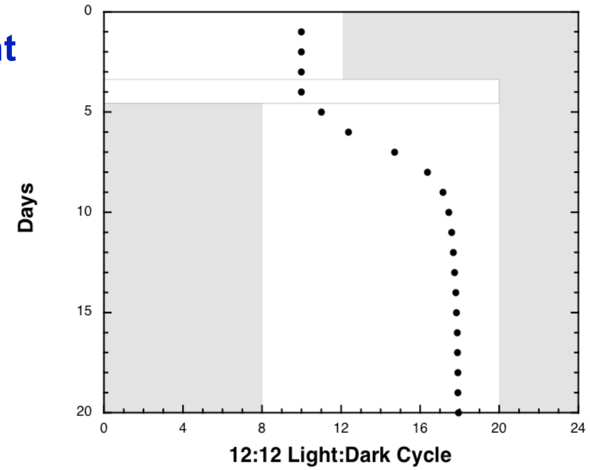


τ > 24h



increased light intensity

Antidromic adjustment



Jet lag

How to Trick Mother Nature into Letting You Fly Around or Stay Up All Night

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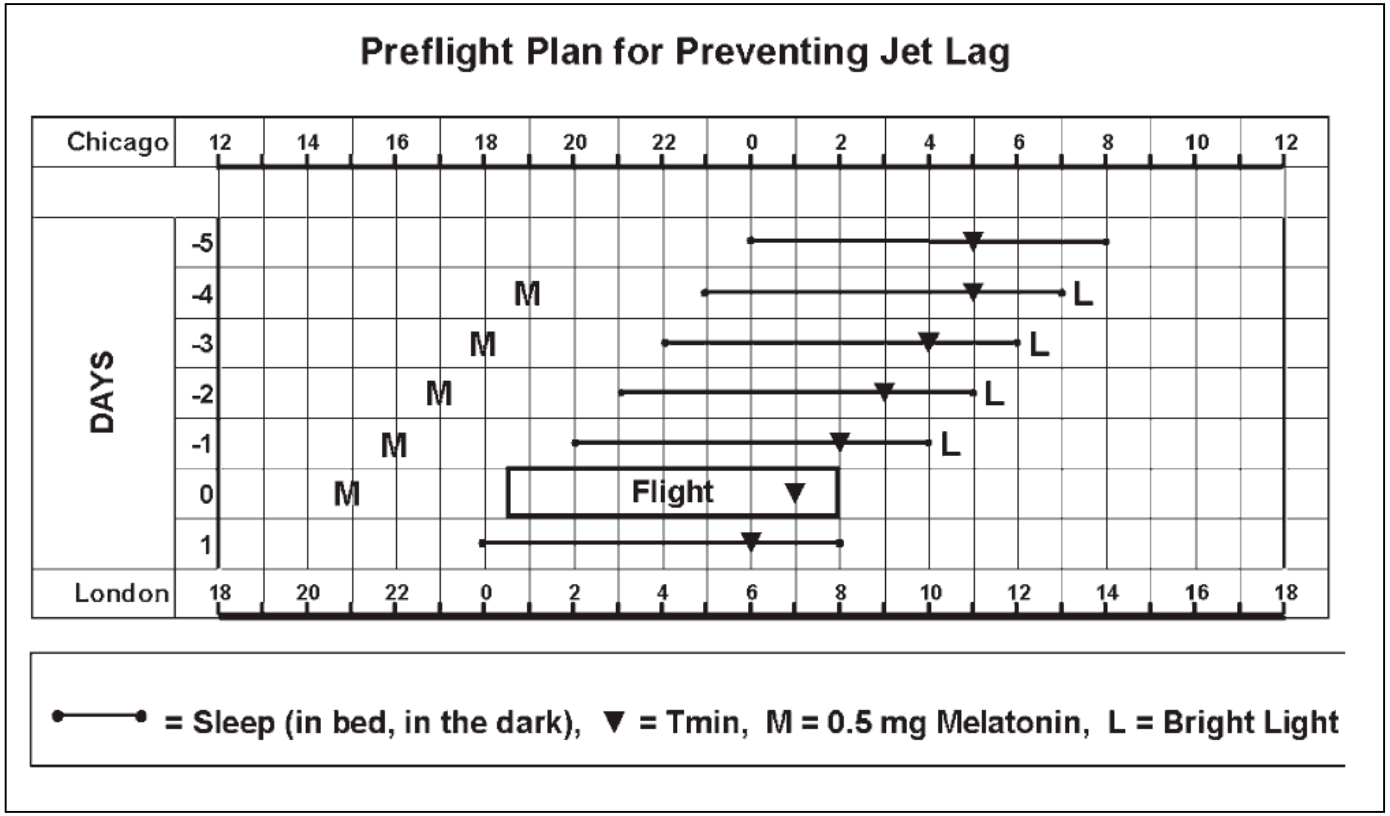

Mammalian circadian clock: summary

Modeling the mammalian circadian clock:

- Analysing and understanding complex situations that become difficult to describe in verbal terms and for which sheer intuition becomes unreliable.

  => Role of the balance PER/CRY for good entrainment

  => Suppression of rhythms by a light pulse

- Rapid exploration of different mechanims and large ranges of conditions.

  => Systematic analysis of the LD condition to have entrainment

- Identification of key interactions and parameters, and their qualitative or quantitative influence for the system's behaviour.

  => Role of nuclear transport rate in *per* mutants in *Drosophila*

  => Role of PER phosphorylation in FASPS

- To address questions that are difficult or impossible to approach experimentally.

  => Design vs robustness to noise

  => Mechanism of synchronization