ULB

# Modeling circadian clocks: From molecular mechanism to physiological disorders

**Albert Goldbeter**
Faculté des Sciences
Université Libre de Bruxelles (ULB)
Brussels, Belgium

*« Living Matter »*
*ICTS, Bangalore, 23 April 2018*

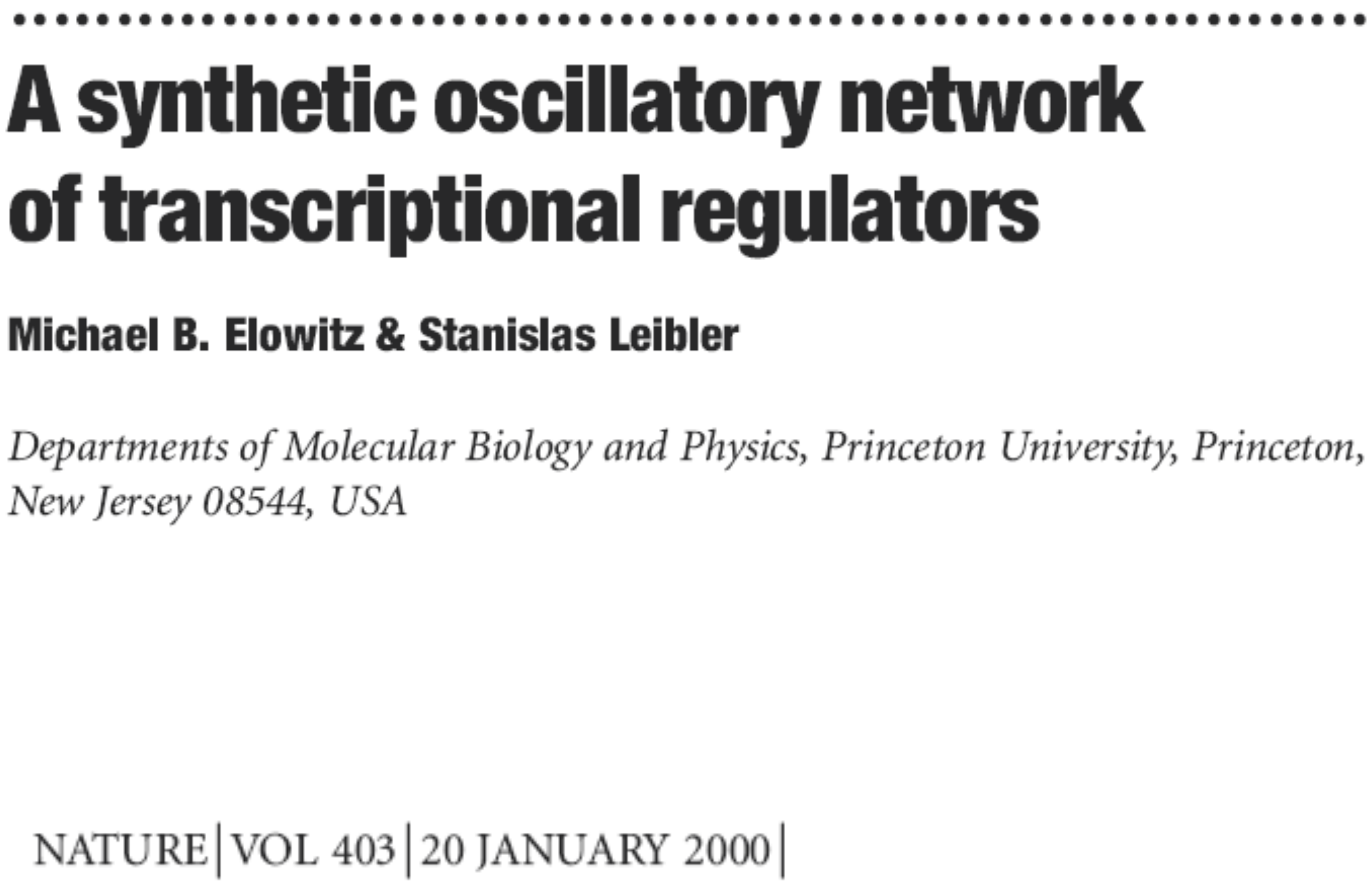
# Main biological rhythms

| Biological rhythm | Period |
|---|---|
| Neural rhythms* | 0.001 s to 10 s |
| Cardiac rhythm* | 1 s |
| Calcium oscillations* | sec to min |
| Biochemical oscillations* | 30 s to 20 min |
| Mitotic oscillator* | 10 min to 24 h |
| Hormonal rhythms* | 10 min to 3-5 h (24 h) |
| Circadian rhythms* | 24 h |
| Ovarian cycle | 28 days (human) |
| Annual rhythms | 1 year |
| Rhythms in ecology and epidemiology | years |

*Cellular rhythms

# Some recently discovered cellular rhythms

| Cellular rhythm | Period |
|---|---|
| Segmentation clock | 30 min - 2h |
| NFκB | 3 h |
| P53 | 3-5 h |
| Msn2 in yeast | 6 min |
| Yeast transcriptome | 40-80 min |
| Synthetic oscillators<br>(e.g., Repressilator) | 3-6 h |

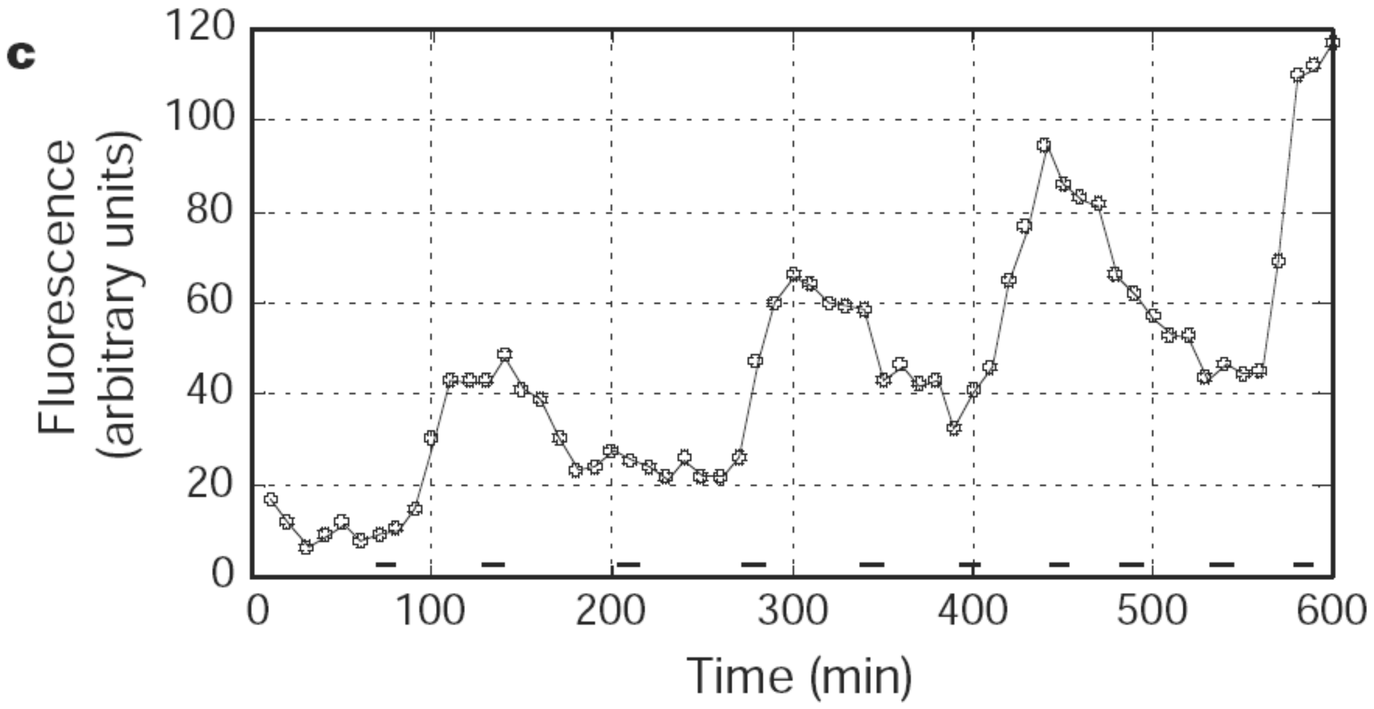


# A synthetic oscillatory network of transcriptional regulators

**Michael B. Elowitz & Stanislas Leibler**

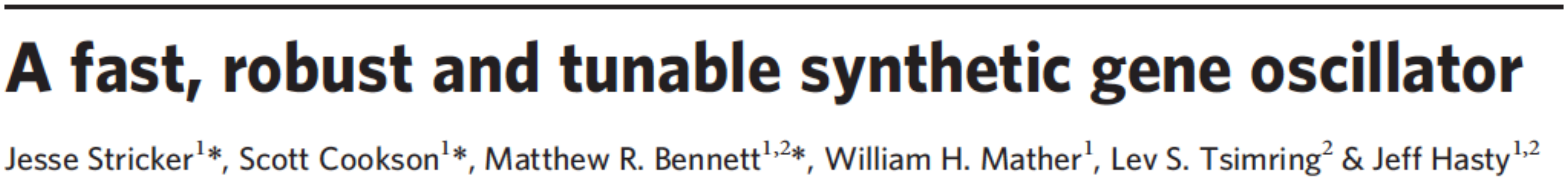
*Departments of Molecular Biology and Physics, Princeton University, Princeton, New Jersey 08544, USA*

NATURE | VOL 403 | 20 JANUARY 2000 |



**Oscillations observed experimentally in the Repressilator**

**Nature (2008)**



# A fast, robust and tunable synthetic gene oscillator

Jesse Stricker[1]*, Scott Cookson[1]*, Matthew R. Bennett[1,2]*, William H. Mather[1], Lev S. Tsimring[2] & Jeff Hasty[1,2]

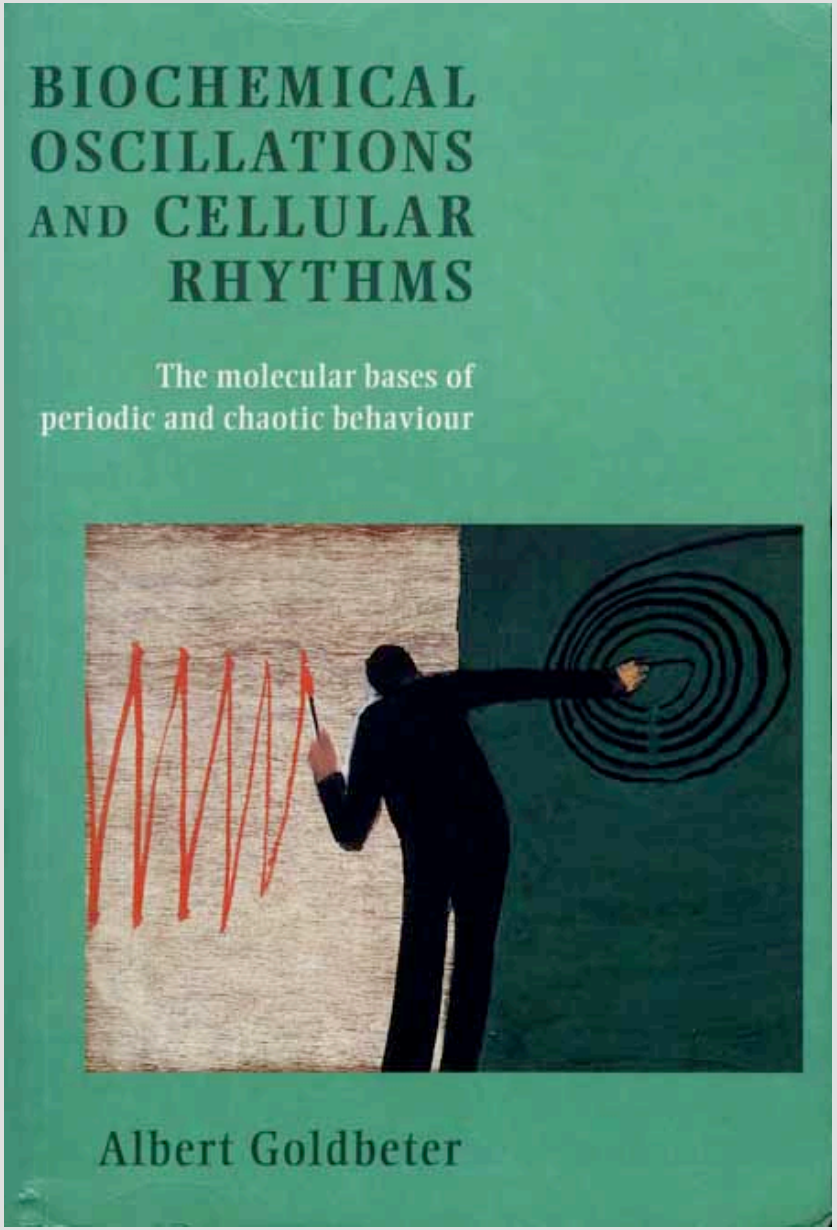
# *FEBS Lett.* 2012

Review

## Systems biology of cellular rhythms

A. Goldbeter *, C. Gérard, D. Gonze, J.-C. Leloup, G. Dupont

*Unité de Chronobiologie théorique, Faculté des Sciences, Université Libre de Bruxelles (ULB), Campus Plaine, CP 231, B-1050 Brussels, Belgium*



BIOCHEMICAL
OSCILLATIONS
AND CELLULAR
RHYTHMS

The molecular bases of
periodic and chaotic behaviour

Albert Goldbeter

1996

# Main biological rhythms

| Biological rhythm | Period |
|---|---|
| Neural rhythms* | 0.001 s to 10 s |
| Cardiac rhythm* | 1 s |
| Calcium oscillations* | sec to min |
| Biochemical oscillations* | 30 s to 20 min |
| Mitotic oscillator* | 10 min to 24 h |
| Hormonal rhythms* | 10 min to 3-5 h (24 h) |
| Circadian rhythms* | 24 h |
| Ovarian cycle | 28 days (human) |
| Annual rhythms | 1 year |
| Rhythms in ecology and epidemiology | years |

*Cellular rhythms

# Modeling circadian clocks :

# From molecular mechanism to physiological disorders

# Circadian rhythms: Physical *versus* molecular models

**Phase model:**

**A. Winfree**

**van der Pol oscillator:**

**R. Wever - R. Kronauer**

# The van der Pol oscillator

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \mu^2\left(y + \left(x - \frac{1}{3}x^3\right)\right)$$

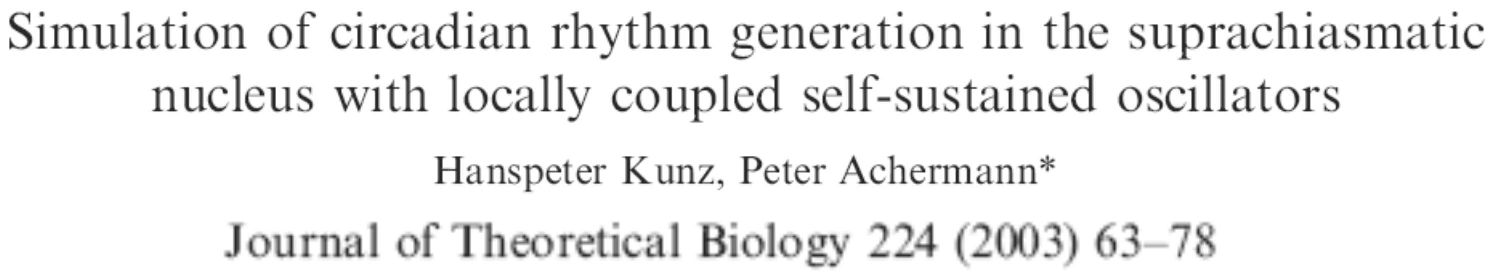
$$\frac{\mathrm{d}y}{\mathrm{d}t} = -x$$

*J Biol Rhythms* (1999) **14**, 532-7.

**A simpler model of the human circadian pacemaker.**

**Forger DB**, **Jewett ME**, **Kronauer RE**.

Numerous studies have used **the classic van der Pol oscillator**, which contains a cubic nonlinearity, to model the effect of light on the human circadian pacemaker. Jewett and Kronauer demonstrated that Aschoff's rule could be incorporated into van der Pol type models and used a van der Pol type oscillator with higher order nonlinearities. Kronauer, Forger, and Jewett have proposed a model for light preprocessing, Process L, representing a biochemical process that converts a light signal into an effective drive on the circadian pacemaker. In the paper presented here, the authors use the classic **van der Pol oscillator** with Process L and Jewett and Kronauer's model of Aschoff's rule to model the human circadian pacemaker. This simpler cubic model predicts the results of a three-pulse human phase response curve experiment and a two-pulse amplitude reduction study with as much, or more, accuracy as the models of Jewett and Kronauer and Kronauer, Forger, and Jewett, which both employ a nonlinearity of degree 7. This suggests that this simpler cubic model should be considered as a potential alternative to other models of the human circadian system currently available.



Simulation of circadian rhythm generation in the suprachiasmatic nucleus with locally coupled self-sustained oscillators

Hanspeter Kunz, Peter Achermann*

Journal of Theoretical Biology 224 (2003) 63–78

# Molecular models for circadian rhythms

3 models of increasing complexity :

**Model I**
**Model II** *for Drosophila*

**Model III** *for the mammalian circadian clock*

→ Link with disorders of the sleep-wake cycle

# Clock mutants of *Drosophila melanogaster*

Ronald J. Konopka & Seymour Benzer

*Proc. Nat. Acad. Sci. USA*
Vol. 68, N°9, pp. 2112-2116, September 1971

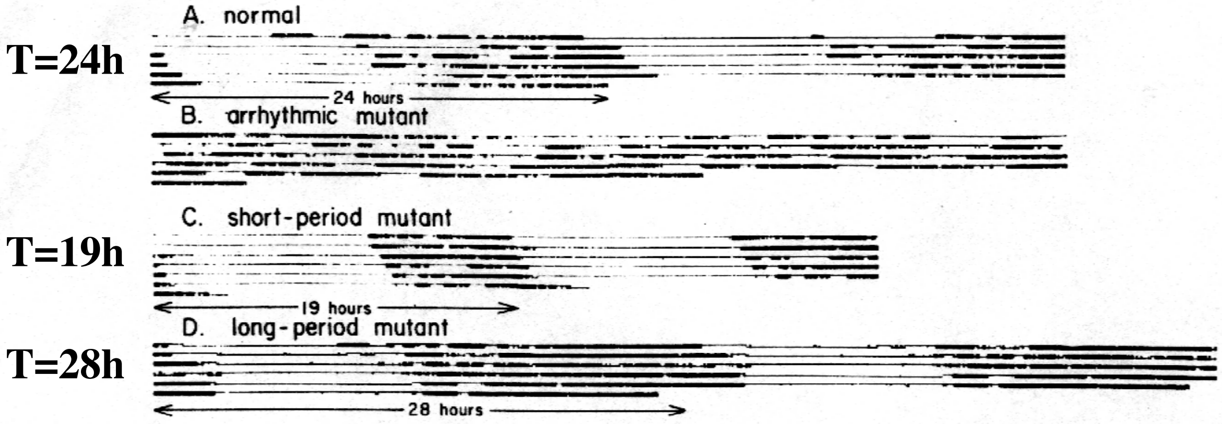
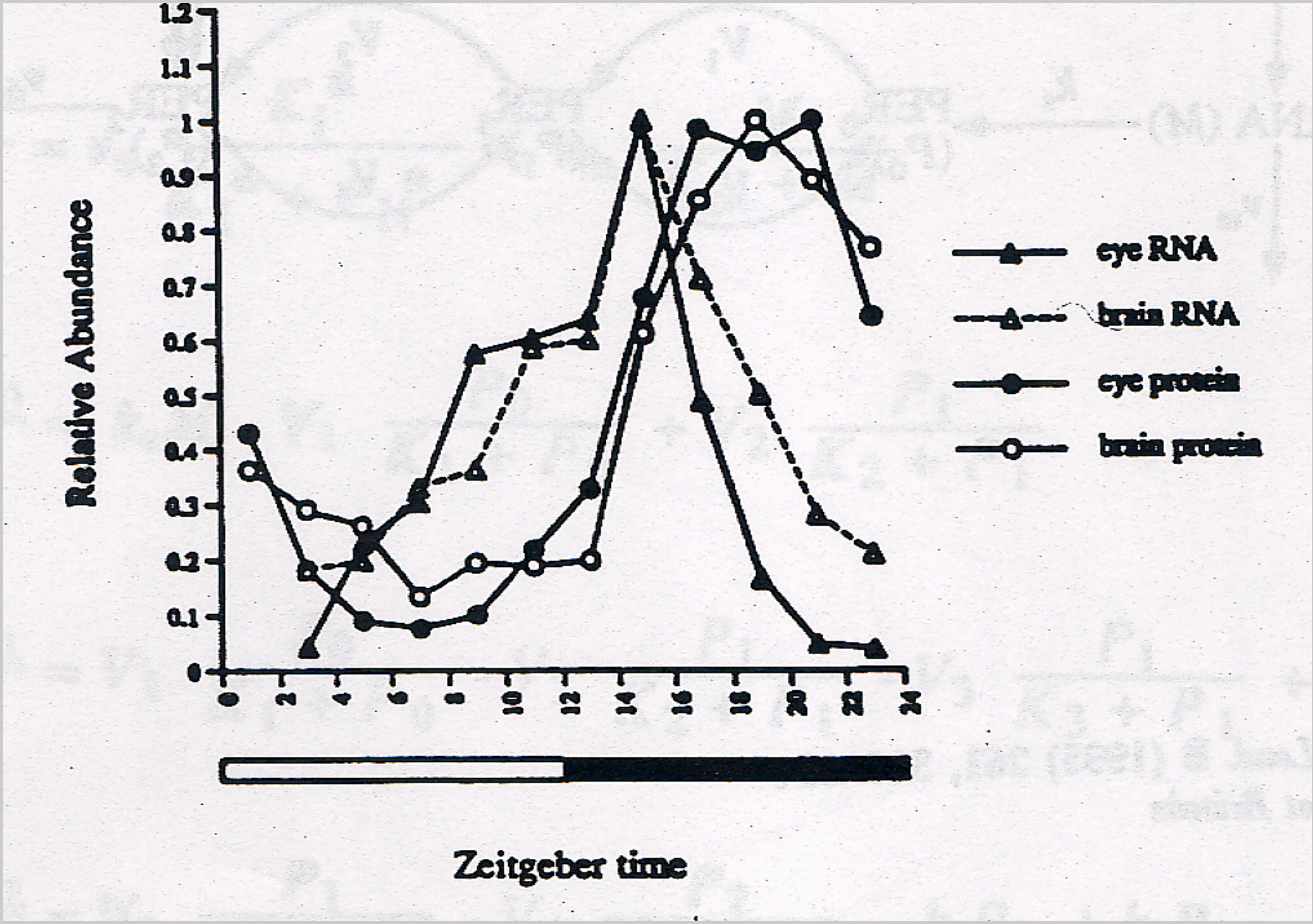
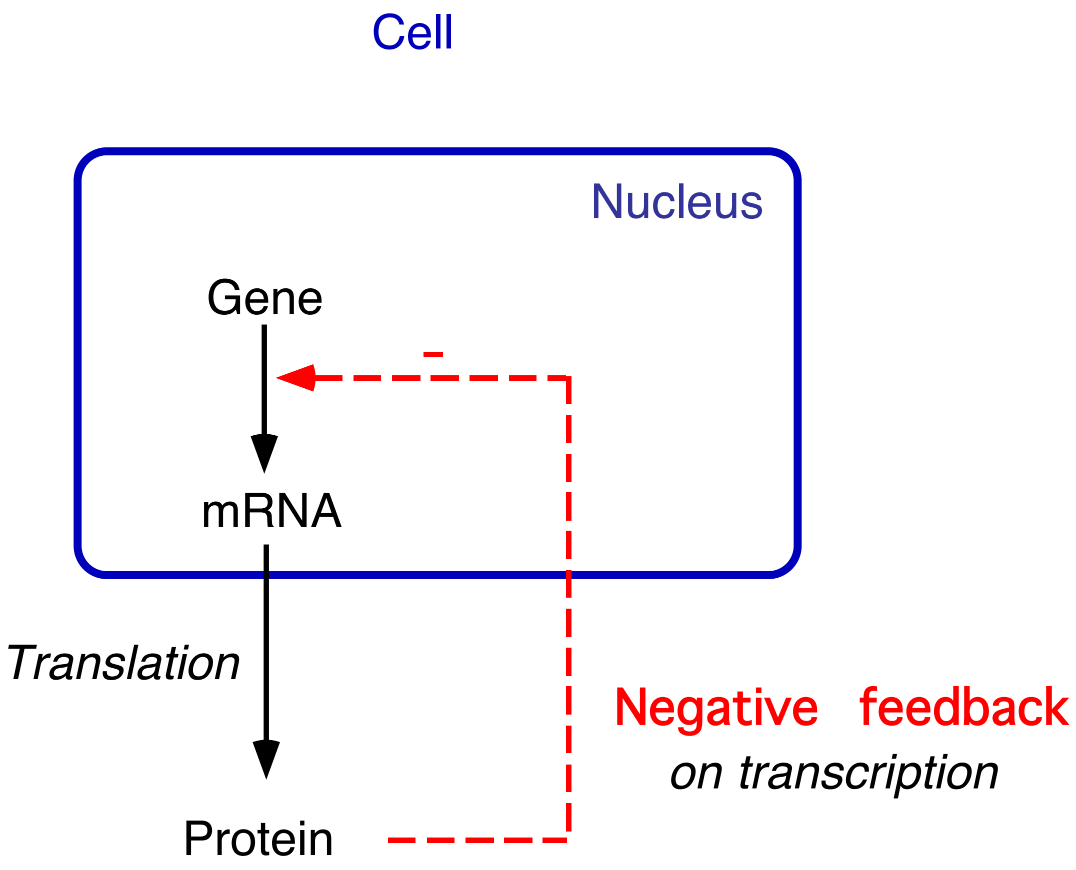


**Fig. 2.** Locomotor activity rhythms, monitored in infrared light, for individual rhythmically normal or mutant flies previously exposed to LD 12:12. Activity registered by event recorder. Records read from *left* to *right*, each new line representing the start of a successive interval. For visual continuity, each successive interval is also replotted to the right of the immediately preceding interval. The traces for normal and arrhythmic are plotted *modulo* 24 hr; for the short-period mutant *modulo* 19 hr is used; the long-period mutant is plotted *modulo* 28 hr. T = 25°C.

# Negative feedback of PER on *per* expression



Zeng, Hardin & Rosbash (1994) *EMBO J*.



Cell

Nucleus

Gene

–

mRNA

*Translation*

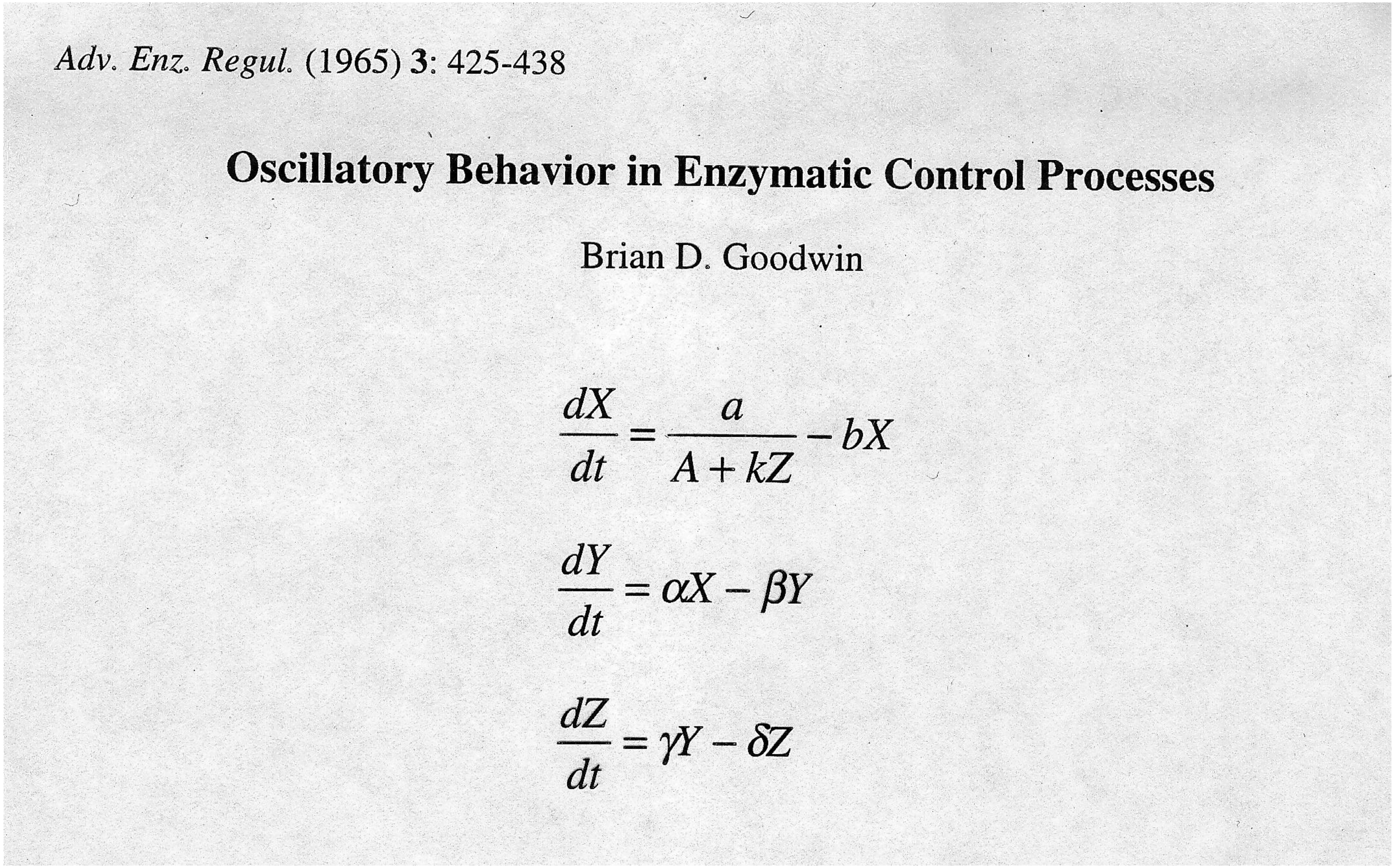
Protein

Negative feedback

*on transcription*

**Core mechanism of circadian rhythms: Negative autoregulation of clock gene expression**

***!!! Other mechanisms: Cyanobacteria (KaiC phosphorylation)***



*Adv. Enz. Regul.* (1965) **3**: 425-438

## Oscillatory Behavior in Enzymatic Control Processes

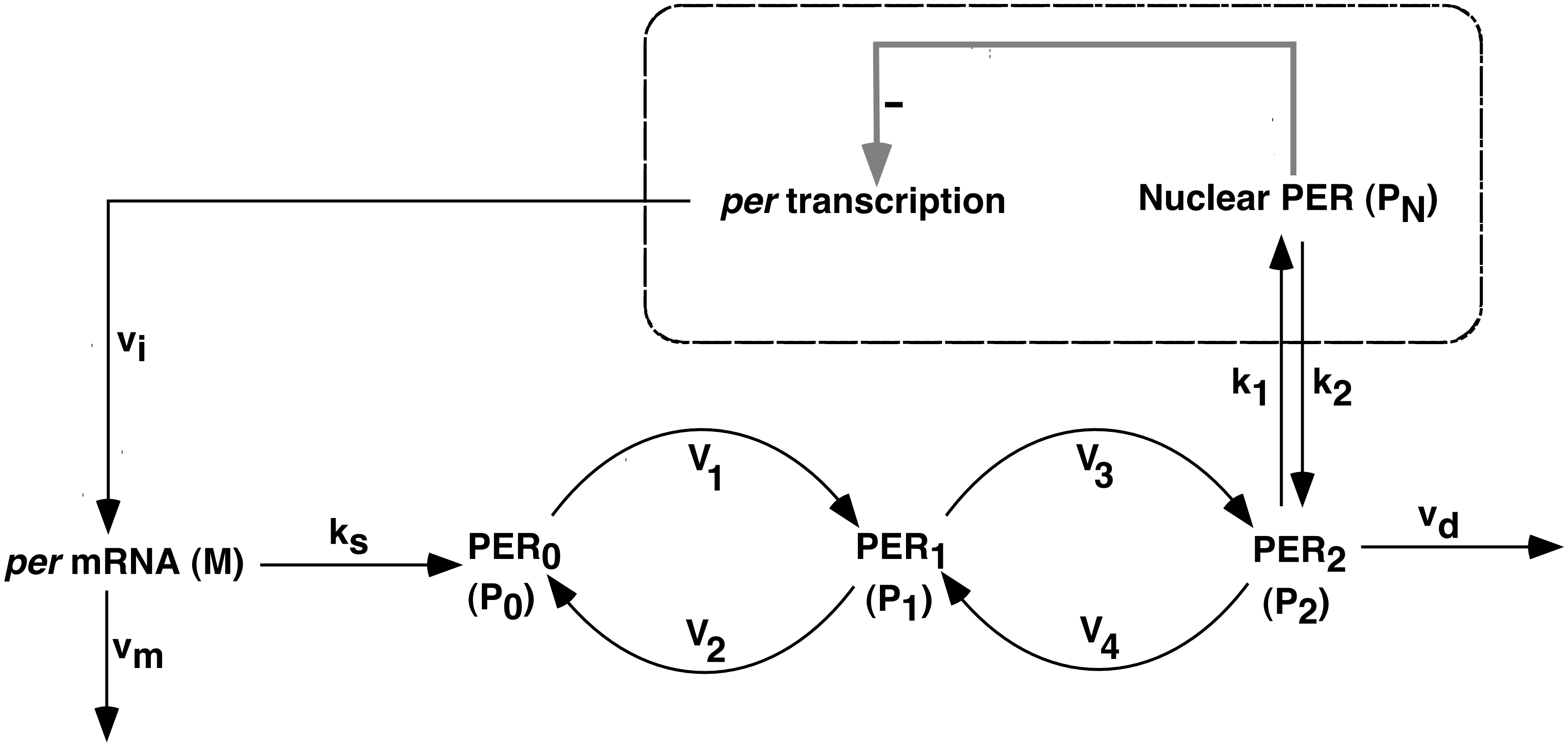
Brian D. Goodwin

$$\frac{dX}{dt} = \frac{a}{A + kZ} - bX$$

$$\frac{dY}{dt} = \alpha X - \beta Y$$

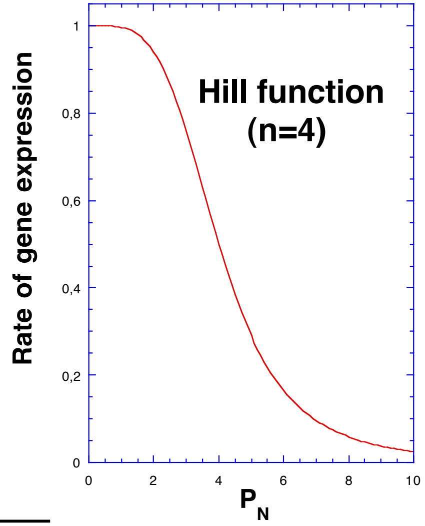
$$\frac{dZ}{dt} = \gamma Y - \delta Z$$

# Model #1 : Negative autoregulation of the *Per* gene by PER



A. Goldbeter (1995). *Proc. R. Soc. Lond. B* 261, 319-324.

# Kinetic equations for the model for PER circadian oscillations



$$\frac{dM}{dt} = v_s \boxed{\frac{K_I^{\,n}}{K_I^{\,n} + P_N^{\,n}}} - v_m \frac{M}{K_{m1} + M}$$

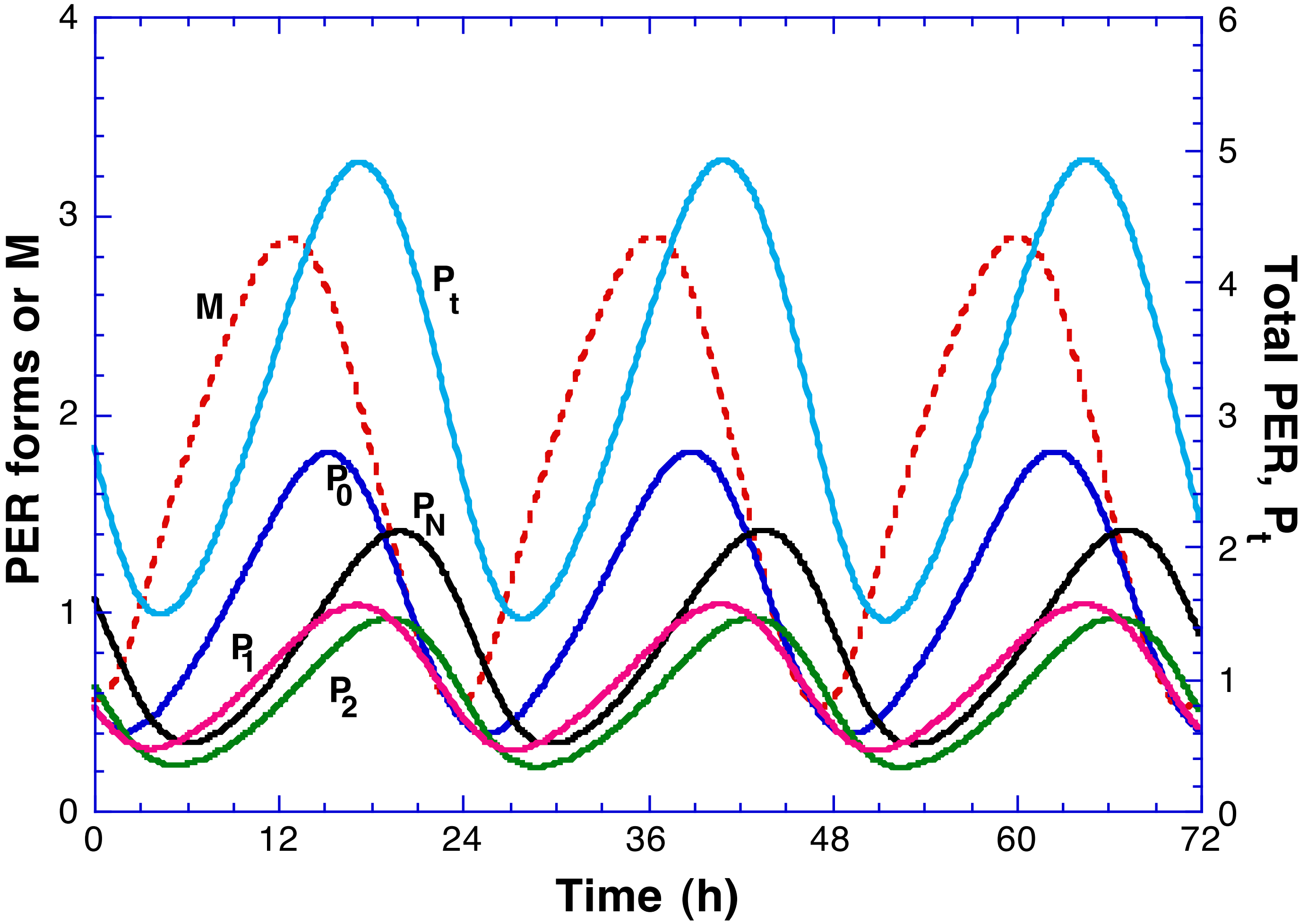
$$\frac{dP_0}{dt} = k_s M - V_1 \frac{P_0}{K_1 + P_0} + V_2 \frac{P_1}{K_2 + P_1}$$

$$\frac{dP_1}{dt} = V_1 \frac{P_0}{K_1 + P_0} - V_2 \frac{P_1}{K_2 + P_1} - V_3 \frac{P_1}{K_3 + P_1} + V_4 \frac{P_2}{K_4 + P_2}$$

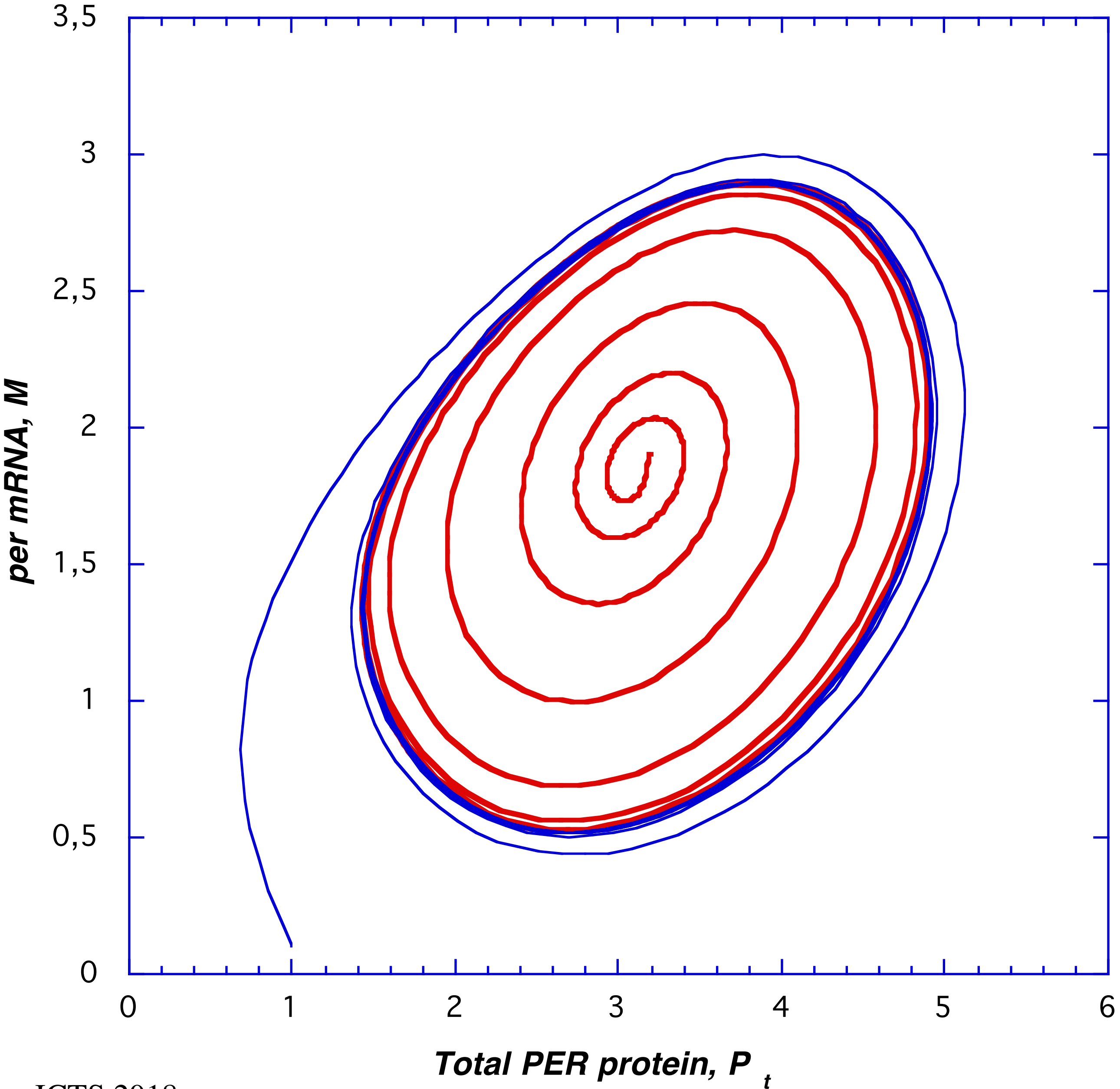
$$\frac{dP_2}{dt} = V_3 \frac{P_1}{K_3 + P_1} - V_4 \frac{P_2}{K_4 + P_2} - k_1 P_2 + k_2 P_N - v_d \frac{P_2}{K_d + P_2}$$

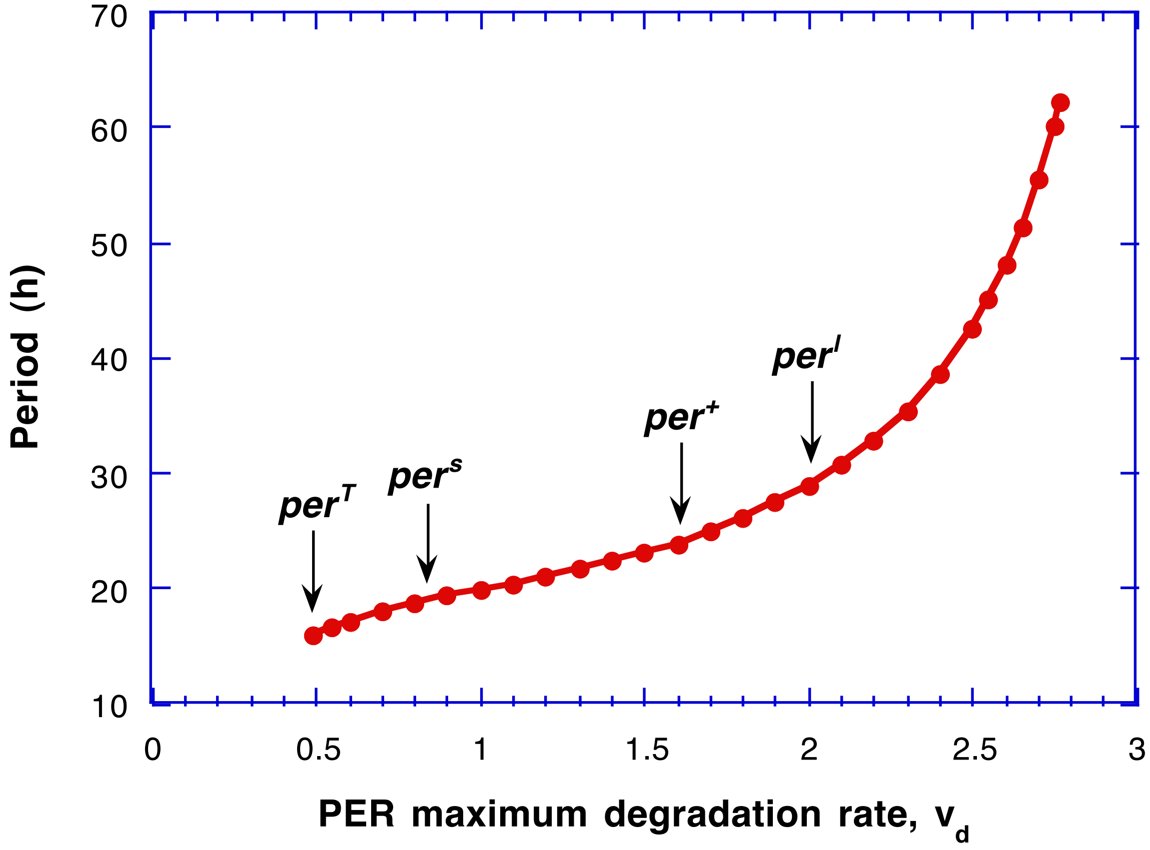
$$\frac{dP_N}{dt} = k_1 P_2 - k_2 P_N$$

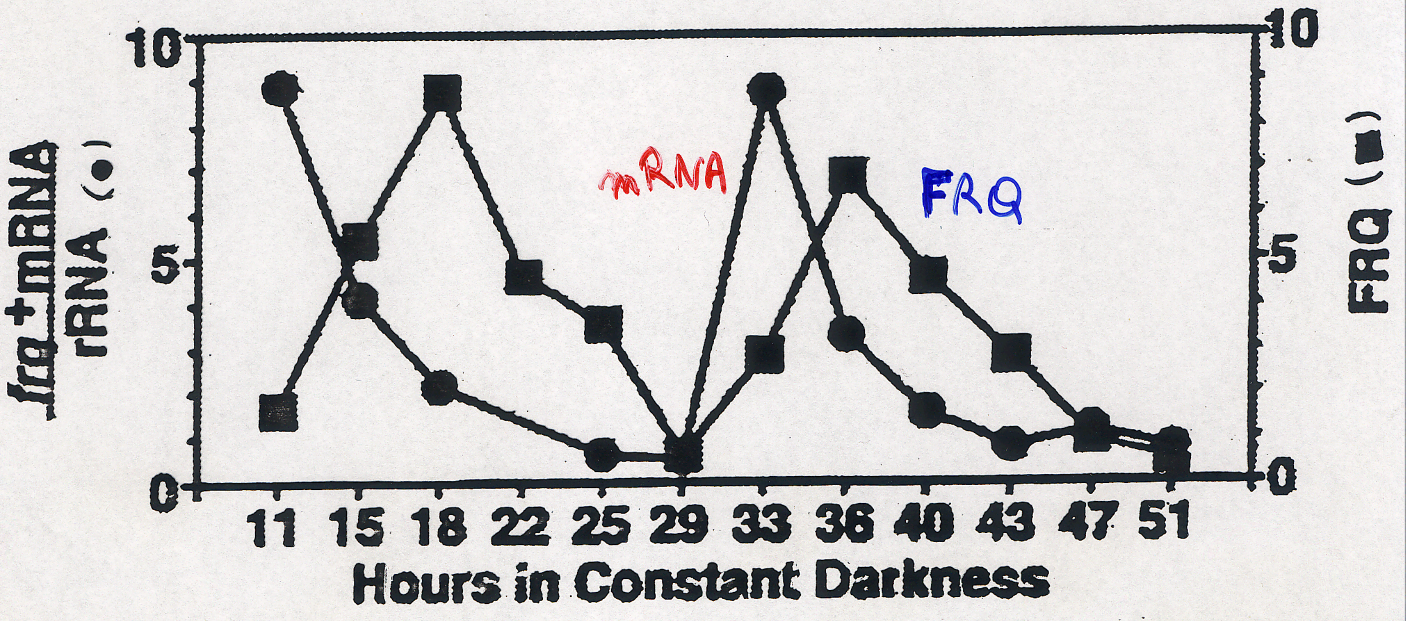
The total (nonconserved) quantity of PER, $P_t$, is given by: $P_t = P_0 + P_1 + P_2 + P_N$



PER forms or M
Total PER, $P_t$
Time (h)
M
$P_t$
$P_0$
$P_N$
$P_1$
$P_2$
0
1
2
3
4
0
1
2
3
4
5
6
0
12
24
36
48
60
72


3,5
3
2,5
2
1,5
1
0,5
0
0
1
2
3
4
5
6
per mRNA, M
Total PER protein, $P_t$

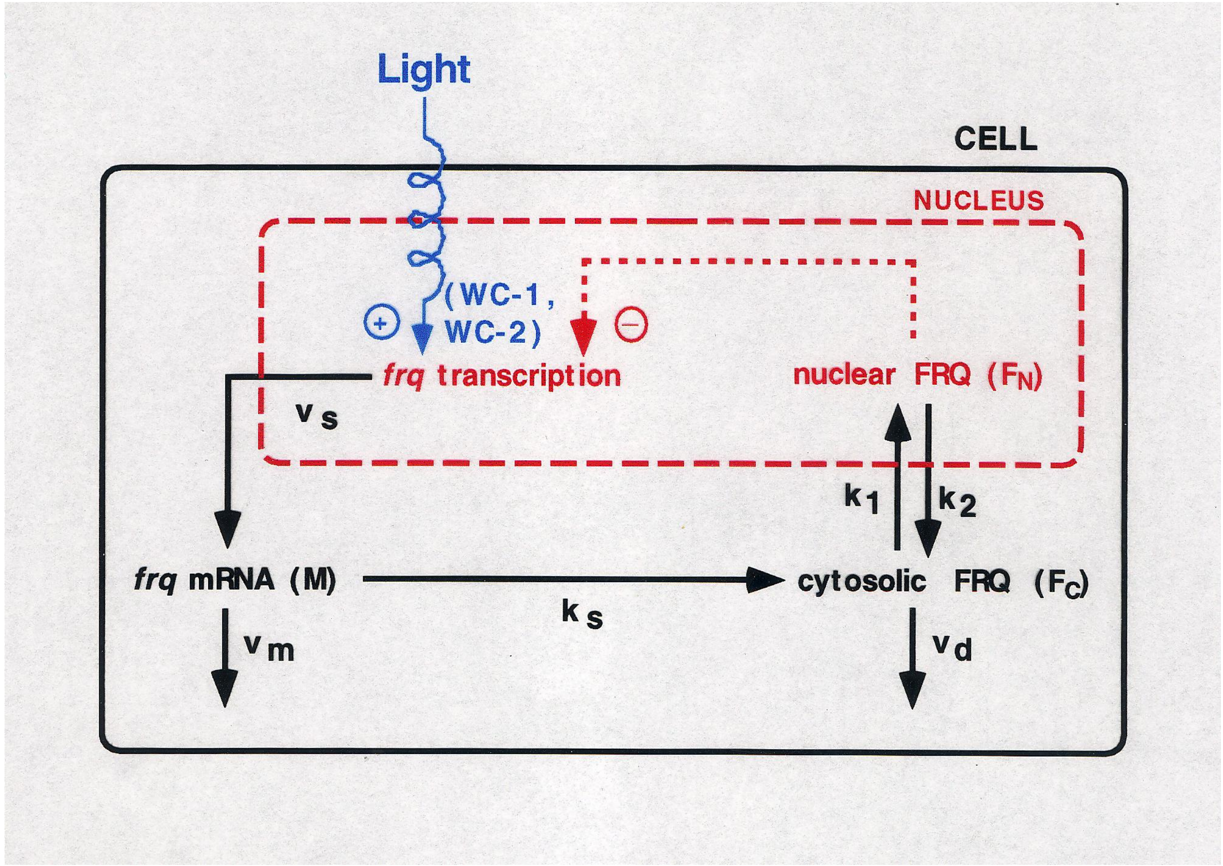

70
60
50
40
30
20
10
Period (h)
0
0.5
1
1.5
2
2.5
3
PER maximum degradation rate, $v_d$
$per^T$
$per^s$
$per^+$
$per^l$



Réf: Garceau et al. (1997) Cell 89:469-47

Garceau et al. (1997) *Cell* **89,** 469.

**Circadian oscillations of *frq* mRNA and FRQ protein in *Neurospora***



# Model for circadian rhythms in *Neurospora*

Leloup et al. (1999)
*J. Biol. Rythms* **14,** 433-448.

$$\frac{dM}{dt} = v_s \frac{K_I^n}{K_I^n + F_N^n} - v_m \frac{M}{K_m + M}$$

$$\frac{dF_C}{dt} = k_s M - v_d \frac{F_C}{K_d + F_C} - k_1 F_C + k_2 F_N$$

$$\frac{dF_N}{dt} = k_1 F_C - k_2 F_N$$

# Circadian rhythms in cyanobacteria:

## DIFFERENT MECHANISM !

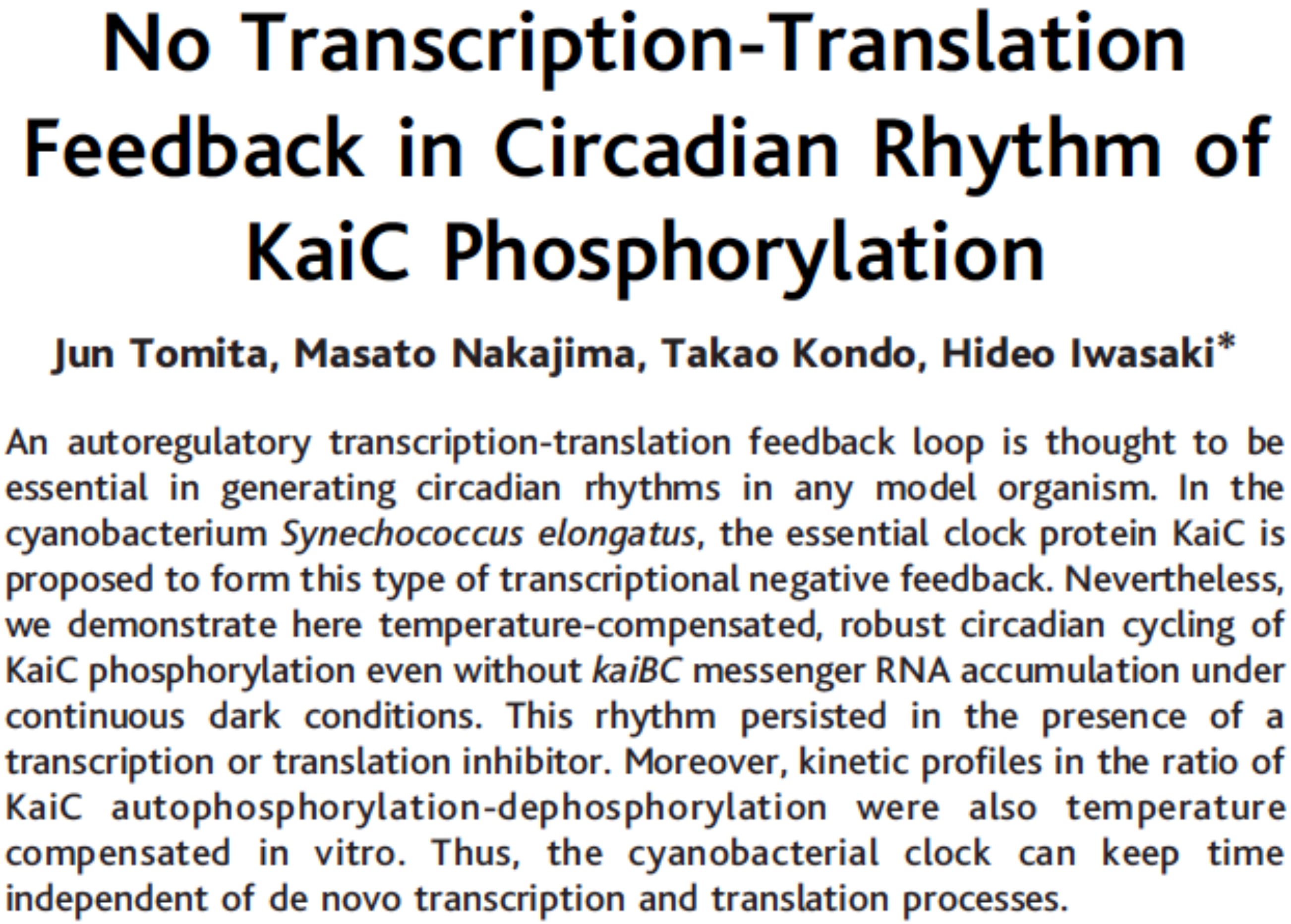
Tomita J. et al (2004) No transcription-translation feedback in circadian rhythm of KaiC phosphorylation. *Science* **307** : 251-254.

Nakajima M et al (2005) Reconstitution of circadian oscillation in cyanobacterial KaiC phosphorylation in vitro. *Science* **308** : 414-415.

Mori T et al (2007) Elucidating the clicking of an in vitro circadian clockwork. *PLoS Biology* 5 : e93.

# *Science* (January 2005)

**Cyanobacteria**



## No Transcription-Translation Feedback in Circadian Rhythm of KaiC Phosphorylation

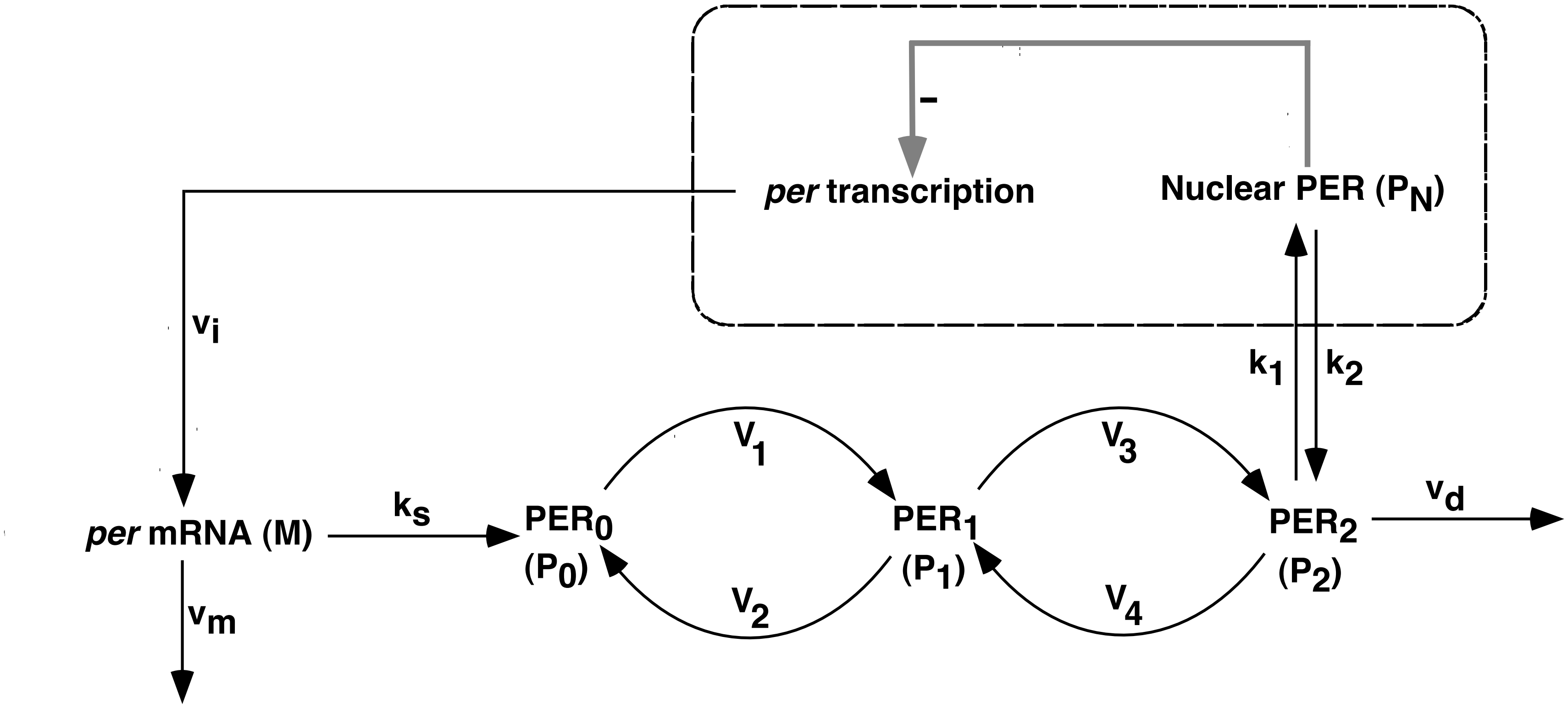
**Jun Tomita, Masato Nakajima, Takao Kondo, Hideo Iwasaki***

An autoregulatory transcription-translation feedback loop is thought to be essential in generating circadian rhythms in any model organism. In the cyanobacterium *Synechococcus elongatus*, the essential clock protein KaiC is proposed to form this type of transcriptional negative feedback. Nevertheless, we demonstrate here temperature-compensated, robust circadian cycling of KaiC phosphorylation even without *kaiBC* messenger RNA accumulation under continuous dark conditions. This rhythm persisted in the presence of a transcription or translation inhibitor. Moreover, kinetic profiles in the ratio of KaiC autophosphorylation-dephosphorylation were also temperature compensated in vitro. Thus, the cyanobacterial clock can keep time independent of de novo transcription and translation processes.

# *Science* (2005)

## Reconstitution of Circadian Oscillation of Cyanobacterial KaiC Phosphorylation in Vitro

**Masato Nakajima, Keiko Imai, Hiroshi Ito, Taeko Nishiwaki, Yoriko Murayama, Hideo Iwasaki, Tokitaka Oyama, Takao Kondo***

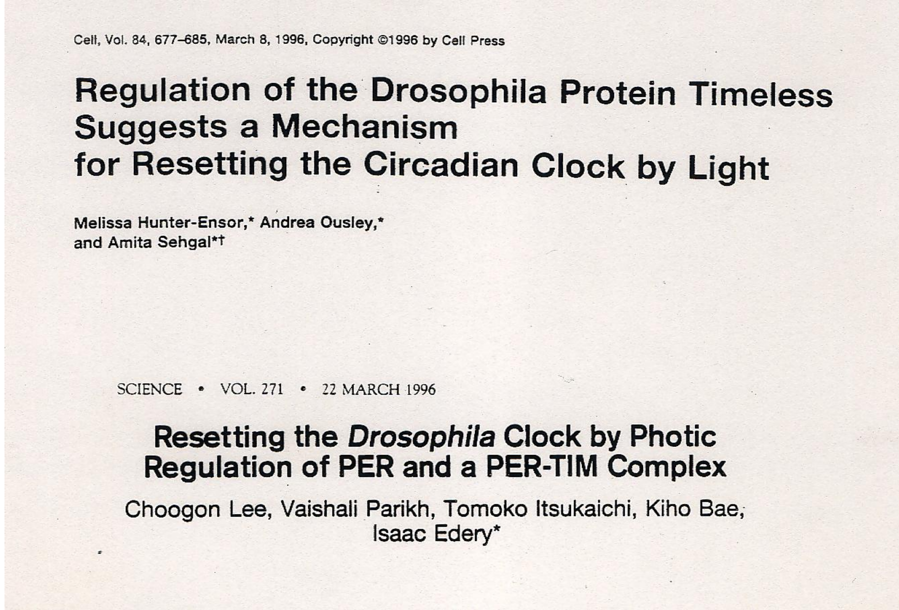


## Effect of light?

A. Goldbeter (1995). *Proc. R. Soc. Lond. B* **261,** 319-324.

A. Goldbeter-ICTS 2018

# Role of TIM in the control of circadian rhythms by light in *Drosophila*



Cell, Vol. 84, 677–685, March 8, 1996, Copyright ©1996 by Cell Press

### Regulation of the Drosophila Protein Timeless Suggests a Mechanism for Resetting the Circadian Clock by Light

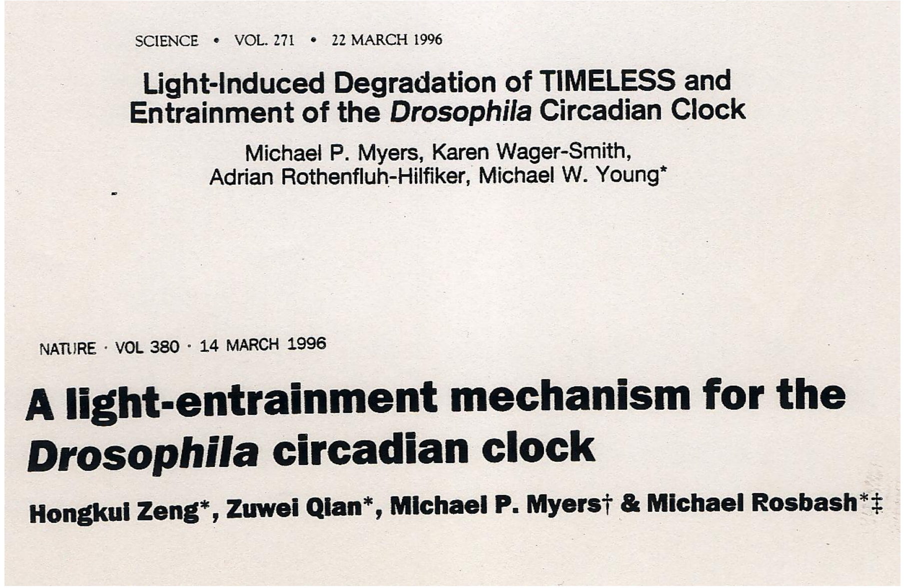
Melissa Hunter-Ensor,* Andrea Ousley,*
and Amita Sehgal*†

---

SCIENCE • VOL. 271 • 22 MARCH 1996

### Resetting the *Drosophila* Clock by Photic Regulation of PER and a PER-TIM Complex

Choogon Lee, Vaishali Parikh, Tomoko Itsukaichi, Kiho Bae,
Isaac Edery*



SCIENCE • VOL. 271 • 22 MARCH 1996

### Light-Induced Degradation of TIMELESS and Entrainment of the *Drosophila* Circadian Clock

Michael P. Myers, Karen Wager-Smith,
Adrian Rothenfluh-Hilfiker, Michael W. Young*

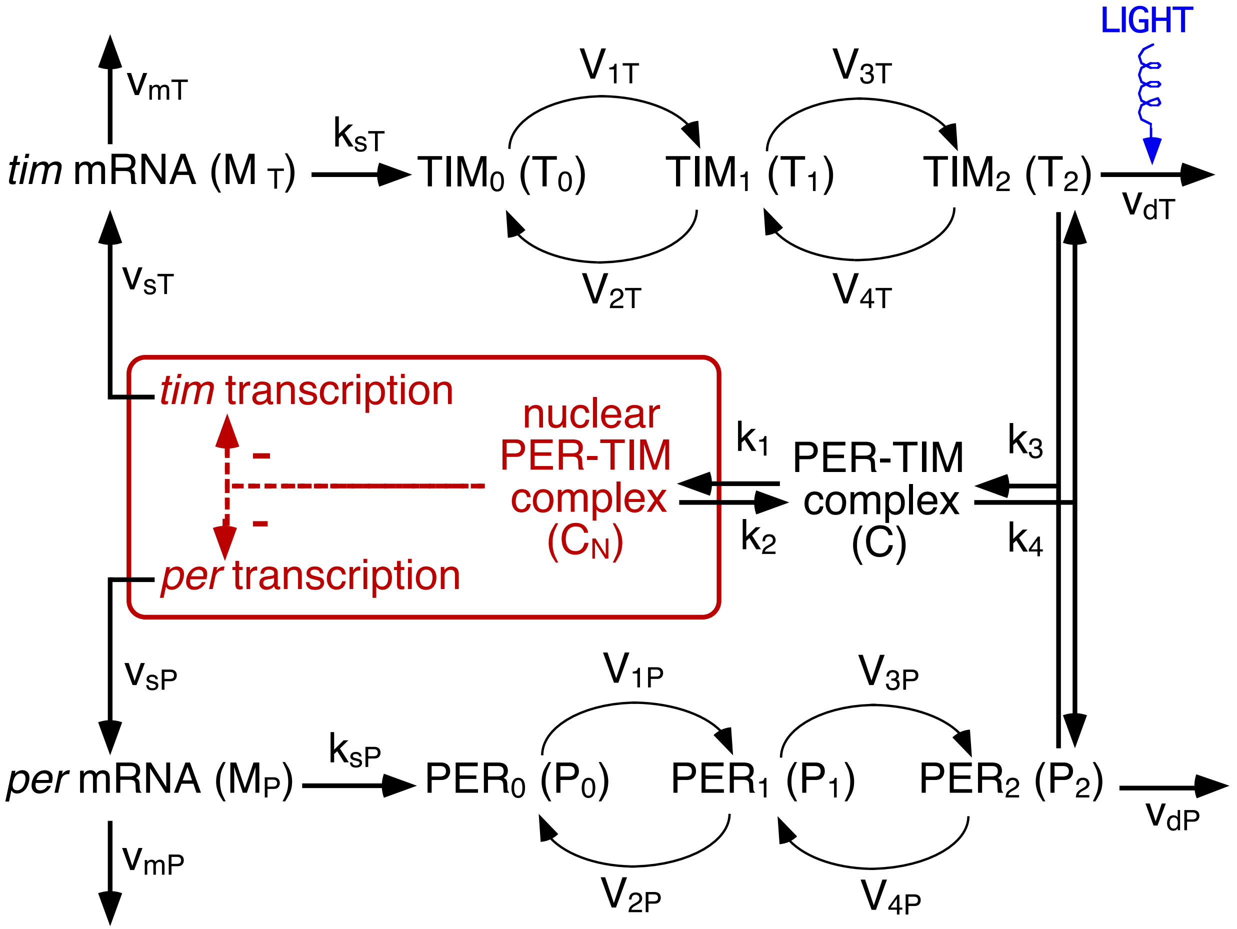
---

NATURE · VOL 380 · 14 MARCH 1996

### A light-entrainment mechanism for the *Drosophila* circadian clock

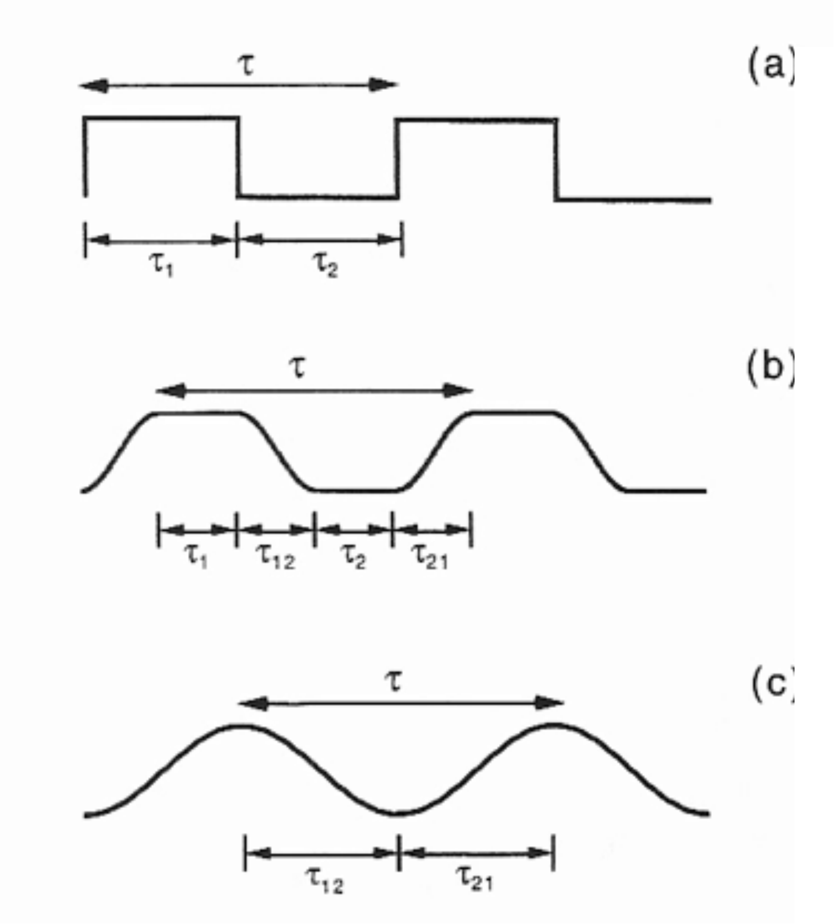
**Hongkui Zeng*, Zuwei Qian*, Michael P. Myers† & Michael Rosbash*‡**

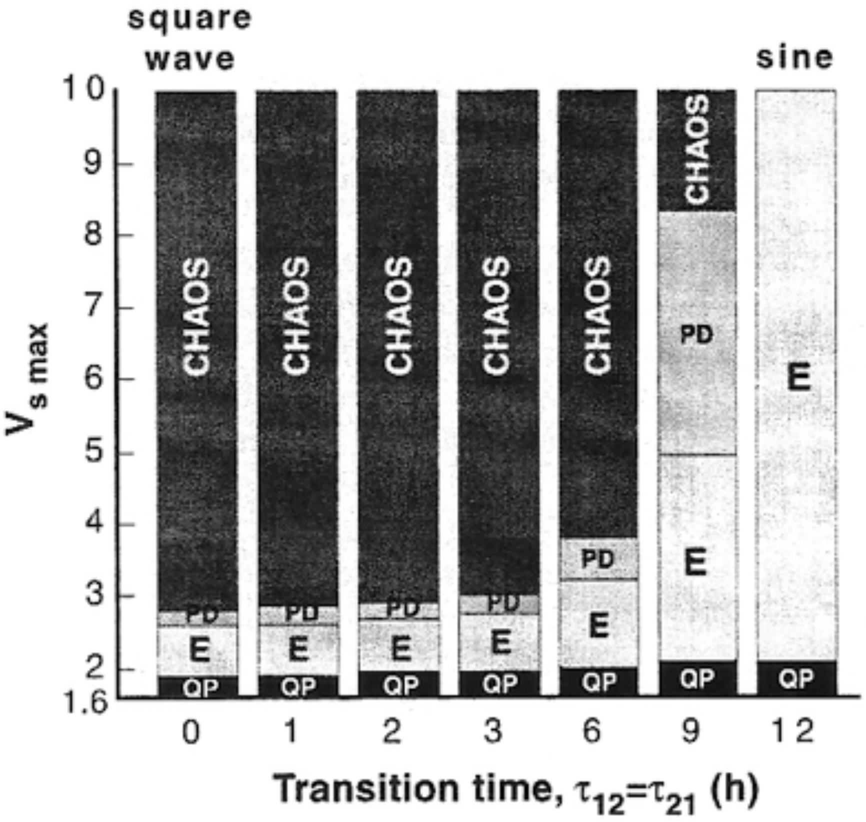
# Model #2 : Incorporating the role of TIM and the effect of light



A model for circadian rhythms in *Drosophila* incorporating the formation of a complex between the PER and TIM proteins J. C. Leloup & A. Goldbeter (1998) *J. Biol. Rhythms* **13:**70-87.

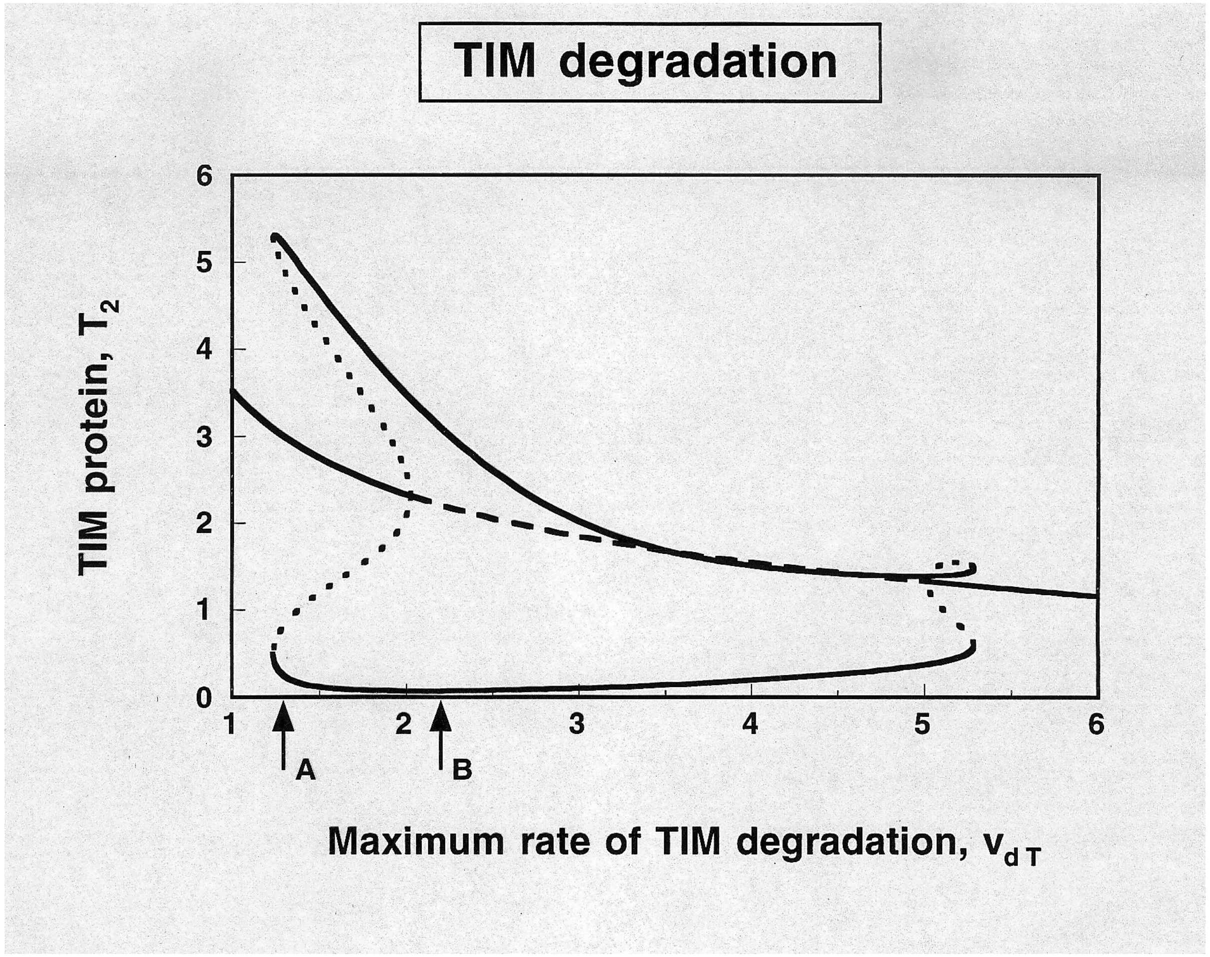
# Nonautonomous chaos: Effect of waveform of LD cycle



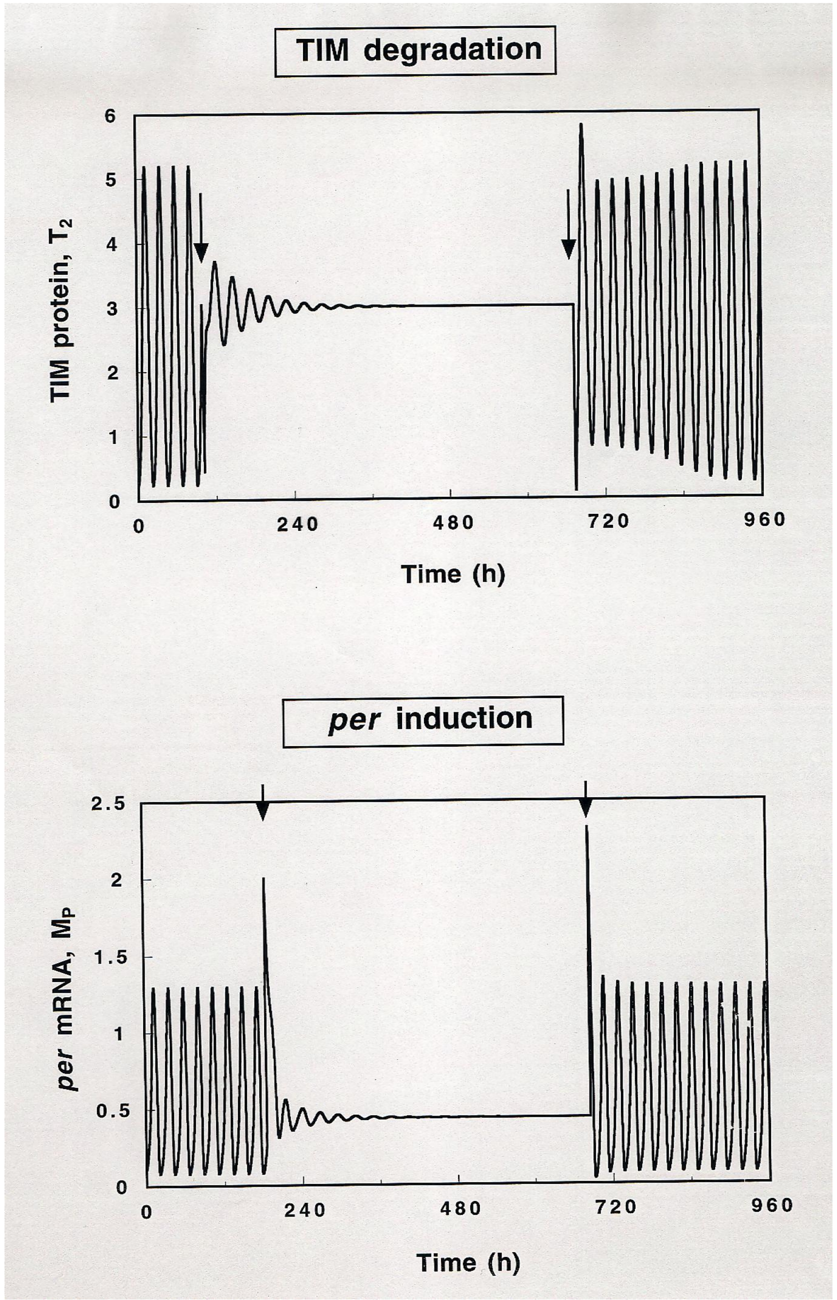


**Gonze & Goldbeter (2000)** ***J. Stat. Phys.***

# Long-term suppression of circadian rhythms by a single pulse of light: Coexistence of a stable steady state with a stable limit cycle

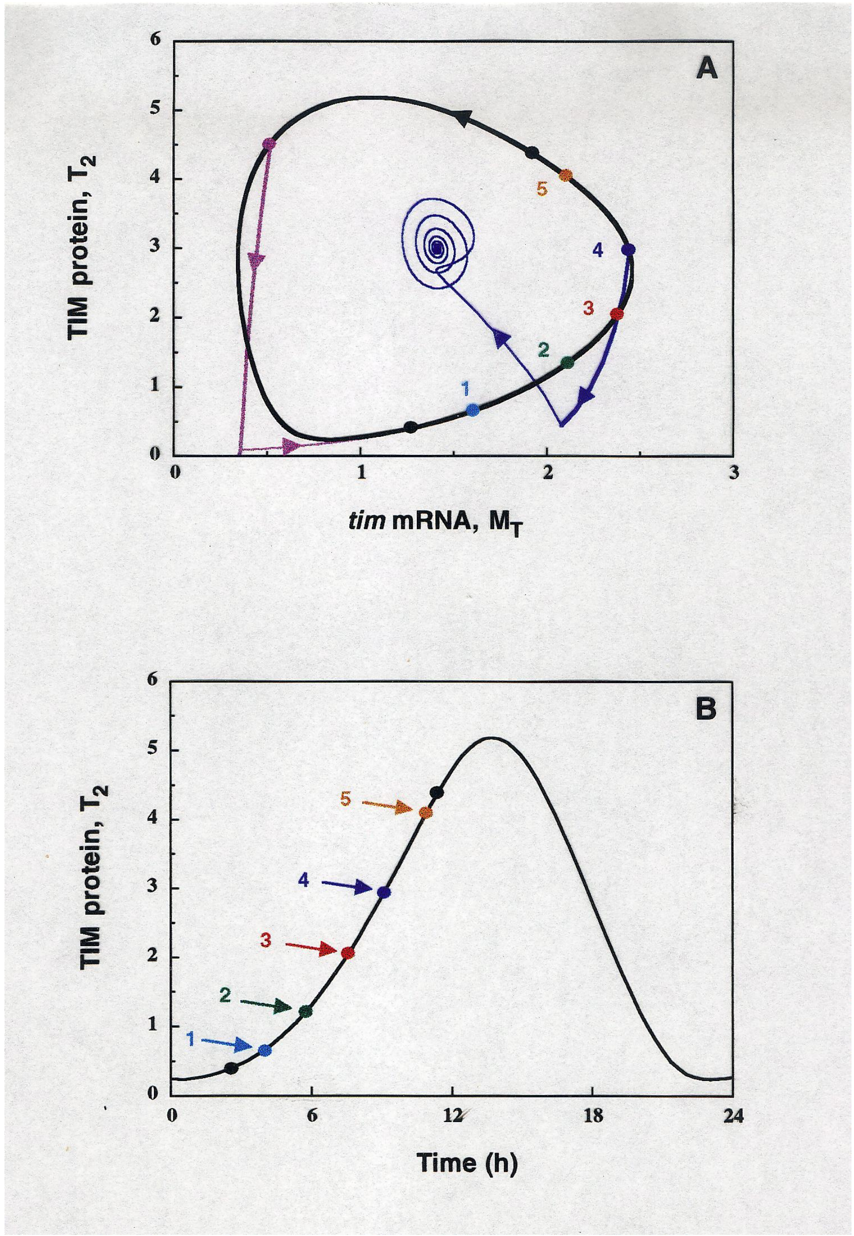


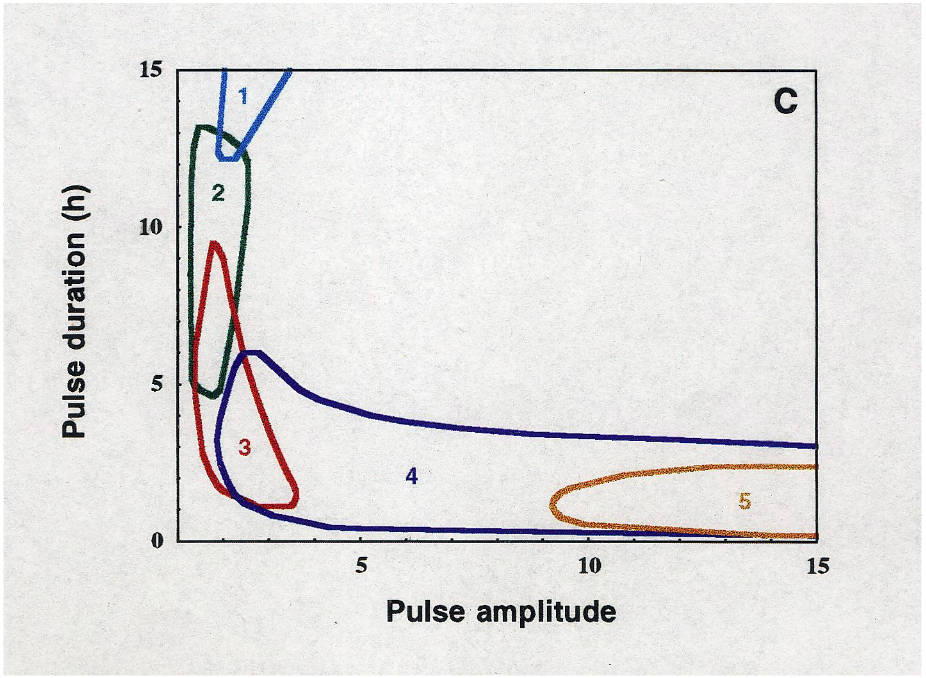
# Long-term suppression of circadian rhythms by a single pulse of light



Leloup & Goldbeter (2001)
*Am. J. Physiol.* 280, R1206-12.

# Long-term suppression of circadian rhythms by a single pulse of light



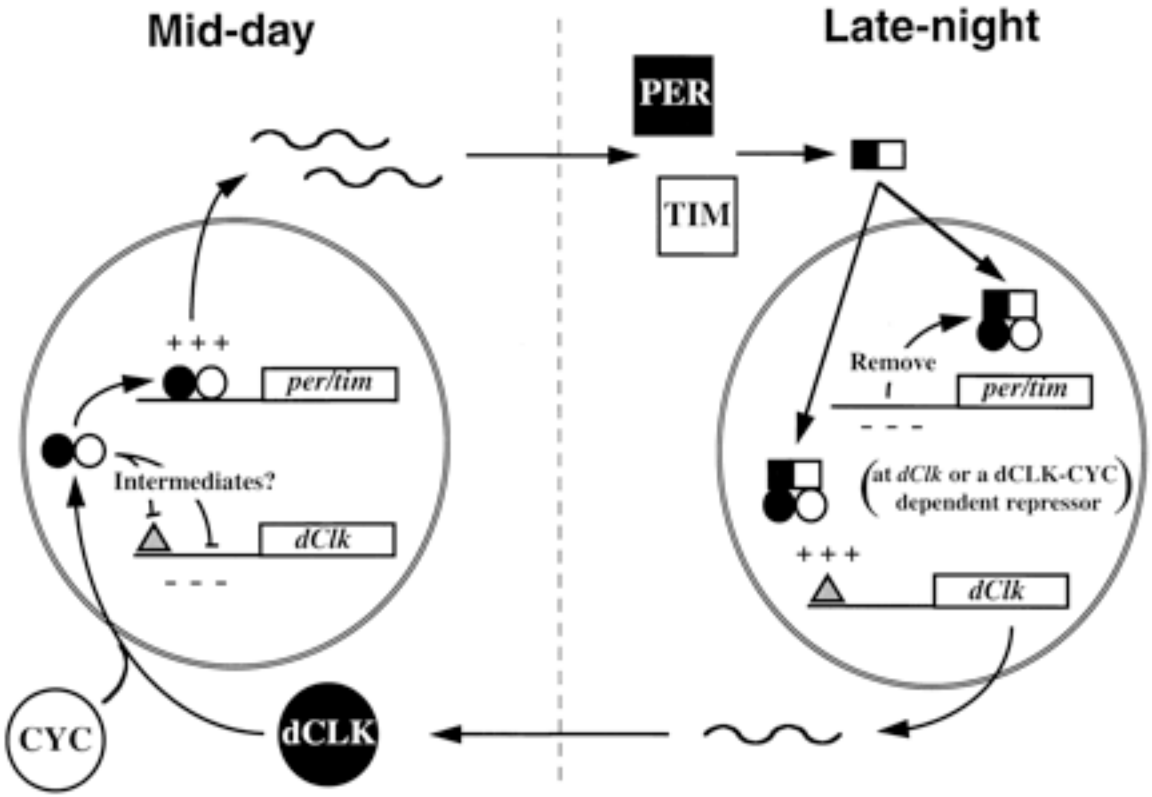


Leloup & Goldbeter (2001)
*Am. J. Physiol.* 280, R1206-12.

*Science* (1999) **286,** 766-8

# Interlocked feedback loops within the Drosophila circadian oscillator.

**Glossop NR, Lyons LC, Hardin PE.**



*J Neurosci.* (2001) **21**: 6644-56.

**Modeling circadian oscillations with interlocking positive and negative feedback loops.**

**Smolen P, Baxter DA, Byrne JH.**

*J Theor Biol.* (2001) **210**: 401-6.

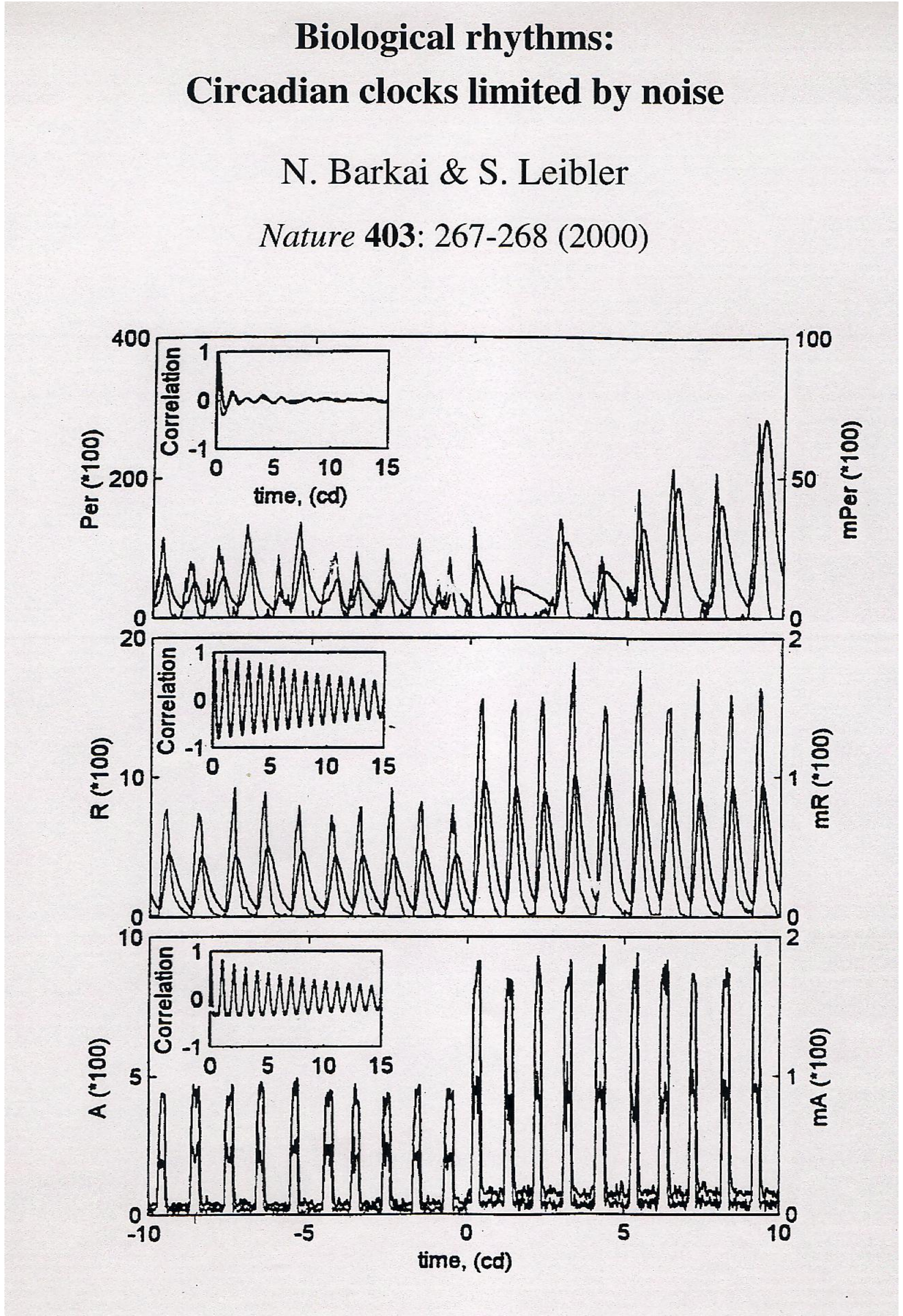
**Robust oscillations within the interlocked feedback model of Drosophila circadian rhythm.**

**Ueda HR, Hagiwara M, Kitano H.**

# **From the *Drosophila* to the mammalian circadian clock**

# Effect of molecular noise

**Stochastic simulations**

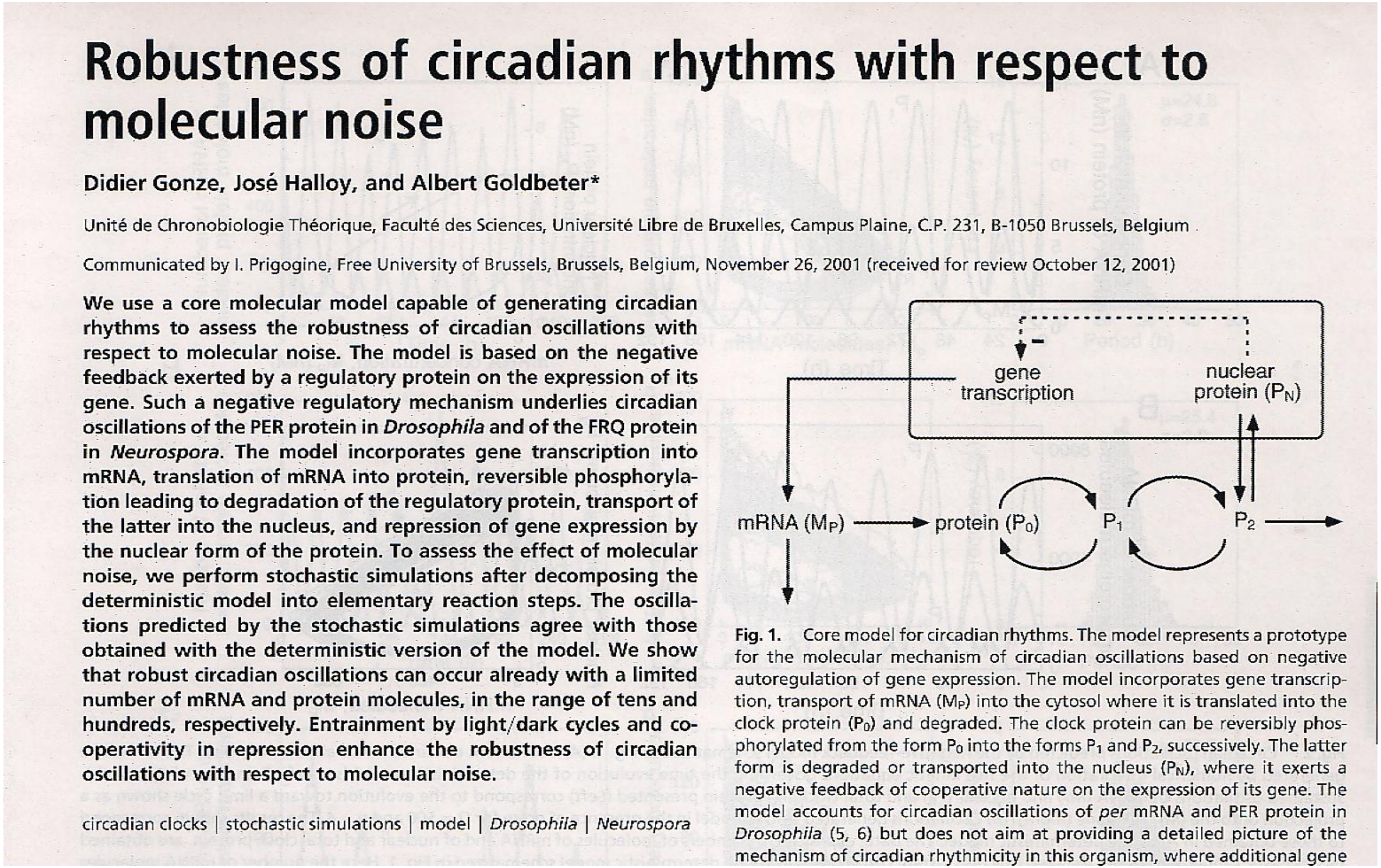


**Biological rhythms:**
**Circadian clocks limited by noise**

N. Barkai & S. Leibler

*Nature* **403**: 267-268 (2000)

*PNAS* **99,** 673-678 (2002)



# Robustness of circadian rhythms with respect to molecular noise

**Didier Gonze, José Halloy, and Albert Goldbeter***

Unité de Chronobiologie Théorique, Faculté des Sciences, Université Libre de Bruxelles, Campus Plaine, C.P. 231, B-1050 Brussels, Belgium

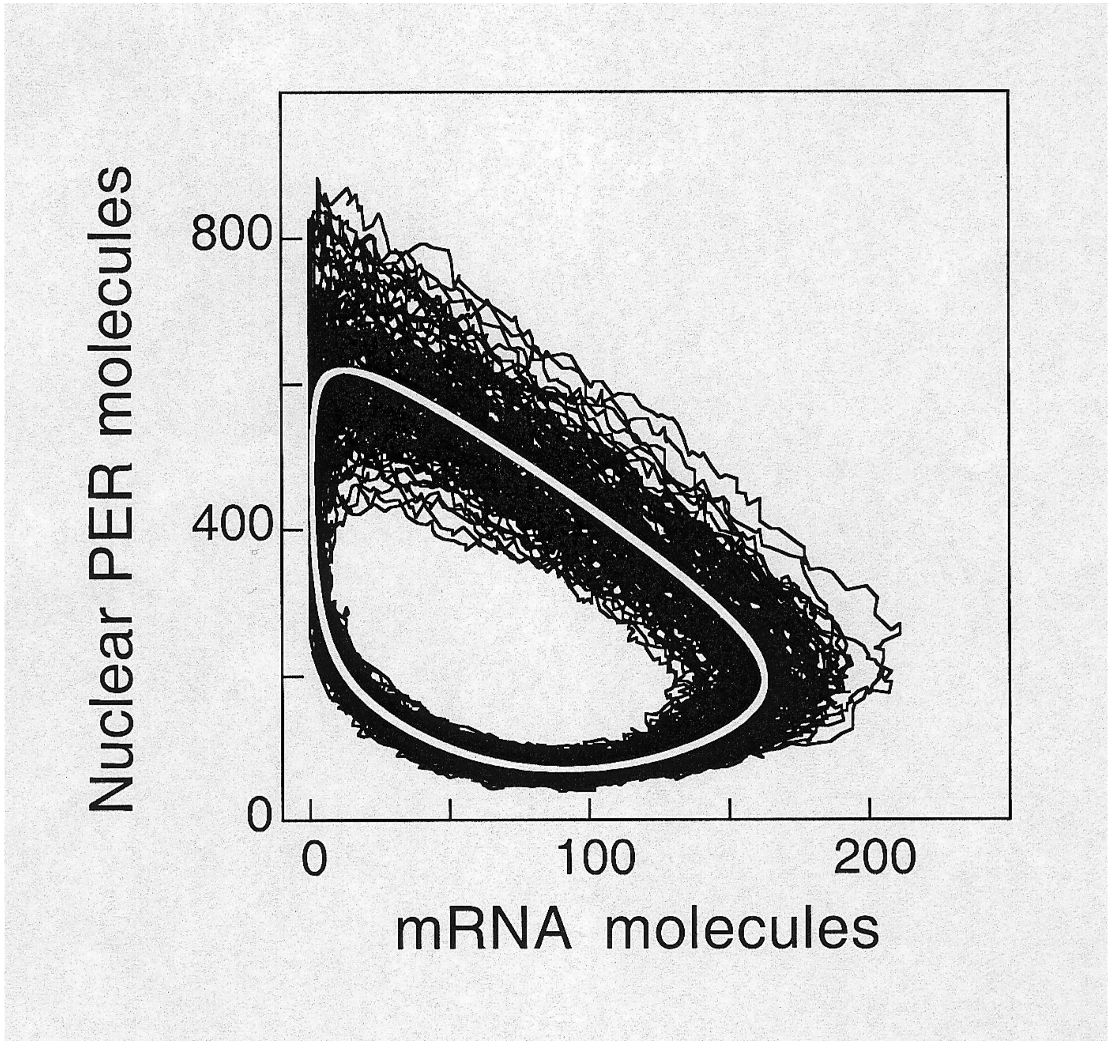
Communicated by I. Prigogine, Free University of Brussels, Brussels, Belgium, November 26, 2001 (received for review October 12, 2001)

**We use a core molecular model capable of generating circadian rhythms to assess the robustness of circadian oscillations with respect to molecular noise. The model is based on the negative feedback exerted by a regulatory protein on the expression of its gene. Such a negative regulatory mechanism underlies circadian oscillations of the PER protein in *Drosophila* and of the FRQ protein in *Neurospora*. The model incorporates gene transcription into mRNA, translation of mRNA into protein, reversible phosphorylation leading to degradation of the regulatory protein, transport of the latter into the nucleus, and repression of gene expression by the nuclear form of the protein. To assess the effect of molecular noise, we perform stochastic simulations after decomposing the deterministic model into elementary reaction steps. The oscillations predicted by the stochastic simulations agree with those obtained with the deterministic version of the model. We show that robust circadian oscillations can occur already with a limited number of mRNA and protein molecules, in the range of tens and hundreds, respectively. Entrainment by light/dark cycles and cooperativity in repression enhance the robustness of circadian oscillations with respect to molecular noise.**

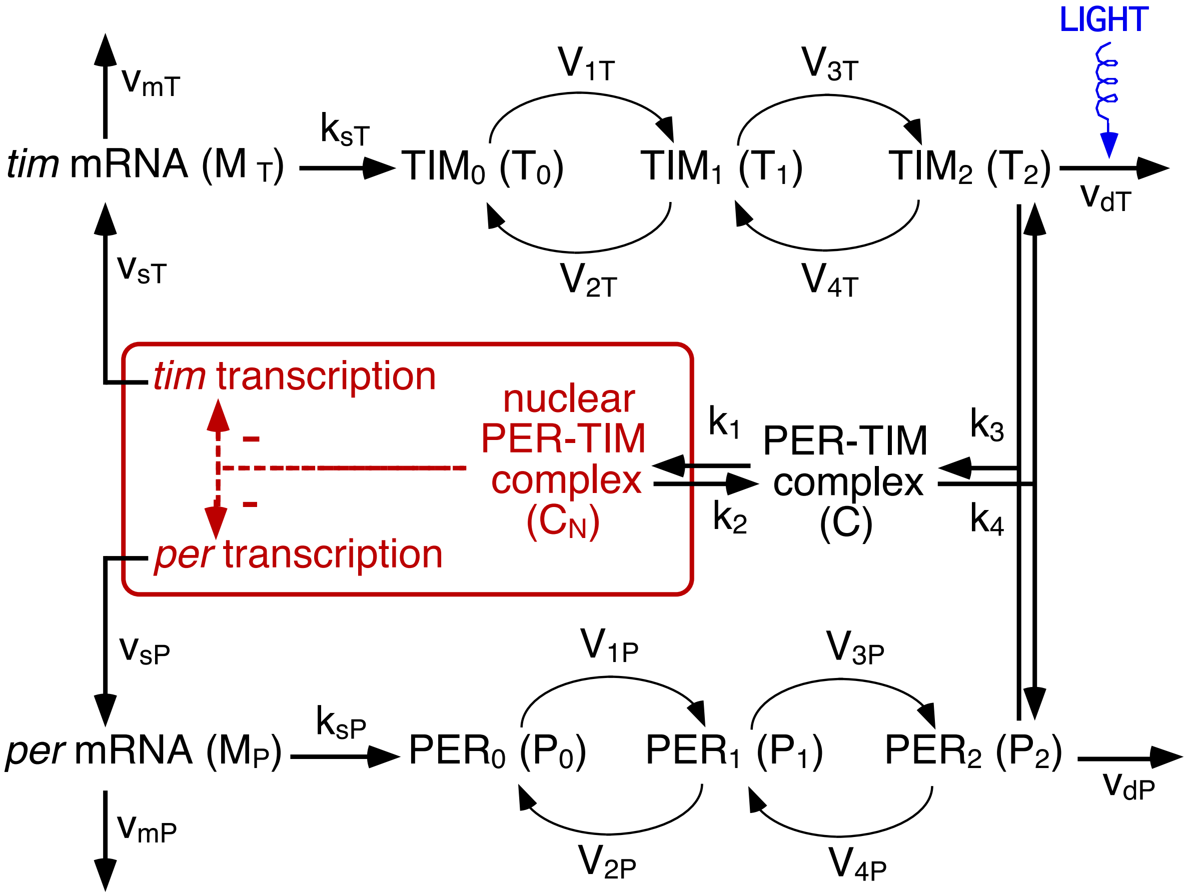
circadian clocks | stochastic simulations | model | *Drosophila* | *Neurospora*

**Fig. 1.** Core model for circadian rhythms. The model represents a prototype for the molecular mechanism of circadian oscillations based on negative autoregulation of gene expression. The model incorporates gene transcription, transport of mRNA ($M_P$) into the cytosol where it is translated into the clock protein ($P_0$) and degraded. The clock protein can be reversibly phosphorylated from the form $P_0$ into the forms $P_1$ and $P_2$, successively. The latter form is degraded or transported into the nucleus ($P_N$), where it exerts a negative feedback of cooperative nature on the expression of its gene. The model accounts for circadian oscillations of *per* mRNA and PER protein in *Drosophila* (5, 6) but does not aim at providing a detailed picture of the mechanism of circadian rhythmicity in this organism, where additional gene

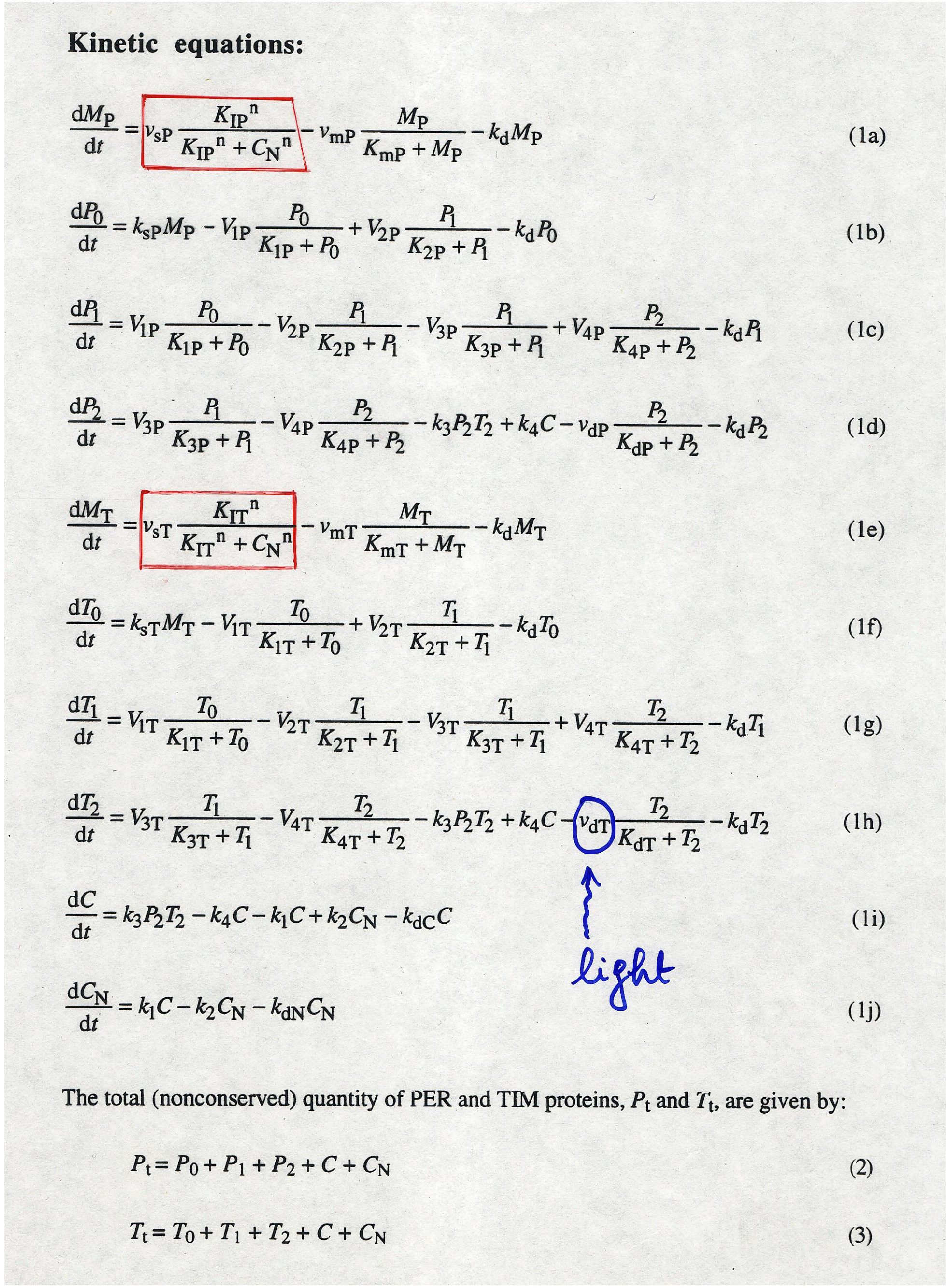
# Noisy limit cycle



# Model #2 : Incorporating the role of TIM and the effect of light



A model for circadian rhythms in *Drosophila* incorporating the formation of a complex between the PER and TIM proteins J. C. Leloup & A. Goldbeter (1998) *J. Biol. Rhythms* **13:**70-87.



**Kinetic equations:**

$$\frac{dM_P}{dt} = \boxed{v_{sP}\frac{K_{IP}^n}{K_{IP}^n + C_N^n}} - v_{mP}\frac{M_P}{K_{mP}+M_P} - k_d M_P \qquad (1a)$$

$$\frac{dP_0}{dt} = k_{sP}M_P - V_{1P}\frac{P_0}{K_{1P}+P_0} + V_{2P}\frac{P_1}{K_{2P}+P_1} - k_d P_0 \qquad (1b)$$

$$\frac{dP_1}{dt} = V_{1P}\frac{P_0}{K_{1P}+P_0} - V_{2P}\frac{P_1}{K_{2P}+P_1} - V_{3P}\frac{P_1}{K_{3P}+P_1} + V_{4P}\frac{P_2}{K_{4P}+P_2} - k_d P_1 \qquad (1c)$$

$$\frac{dP_2}{dt} = V_{3P}\frac{P_1}{K_{3P}+P_1} - V_{4P}\frac{P_2}{K_{4P}+P_2} - k_3P_2T_2 + k_4C - v_{dP}\frac{P_2}{K_{dP}+P_2} - k_d P_2 \qquad (1d)$$

$$\frac{dM_T}{dt} = \boxed{v_{sT}\frac{K_{IT}^n}{K_{IT}^n + C_N^n}} - v_{mT}\frac{M_T}{K_{mT}+M_T} - k_d M_T \qquad (1e)$$

$$\frac{dT_0}{dt} = k_{sT}M_T - V_{1T}\frac{T_0}{K_{1T}+T_0} + V_{2T}\frac{T_1}{K_{2T}+T_1} - k_d T_0 \qquad (1f)$$

$$\frac{dT_1}{dt} = V_{1T}\frac{T_0}{K_{1T}+T_0} - V_{2T}\frac{T_1}{K_{2T}+T_1} - V_{3T}\frac{T_1}{K_{3T}+T_1} + V_{4T}\frac{T_2}{K_{4T}+T_2} - k_d T_1 \qquad (1g)$$

$$\frac{dT_2}{dt} = V_{3T}\frac{T_1}{K_{3T}+T_1} - V_{4T}\frac{T_2}{K_{4T}+T_2} - k_3P_2T_2 + k_4C - \underset{\underset{\text{light}}{\uparrow}}{\boxed{v_{dT}}}\frac{T_2}{K_{dT}+T_2} - k_d T_2 \qquad (1h)$$

$$\frac{dC}{dt} = k_3P_2T_2 - k_4C - k_1C + k_2C_N - k_{dC}C \qquad (1i)$$

$$\frac{dC_N}{dt} = k_1C - k_2C_N - k_{dN}C_N \qquad (1j)$$

The total (nonconserved) quantity of PER and TIM proteins, $P_t$ and $T_t$, are given by:

$$P_t = P_0 + P_1 + P_2 + C + C_N \qquad (2)$$

$$T_t = T_0 + T_1 + T_2 + C + C_N \qquad (3)$$

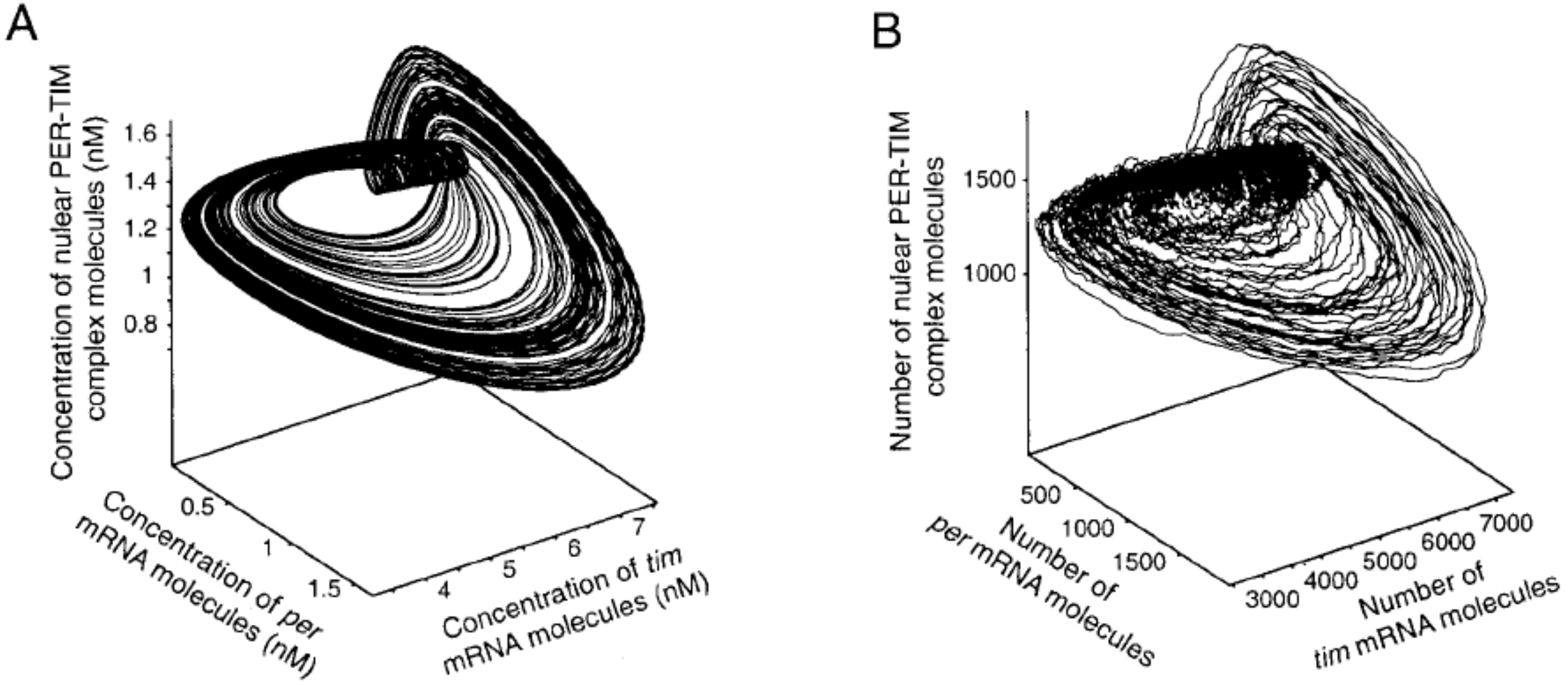


**FIGURE 4.** Effect of molecular noise on autonomous chaos. The strange attractor predicted [26] by the 10-variable deterministic model for circadian rhythms (A) is recovered in (B) by stochastic simulations [22].

**Gonze D, Halloy J, Leloup J-C, Goldbeter A** (2003) Stochastic models for circadian rhythms: effect of molecular noise on periodic and chaotic behavior. *C. R. Biologies*. 326: 189-203.

# Circadian rhythms in mammals:

# Pacemaker role of suprachiasmatic nuclei

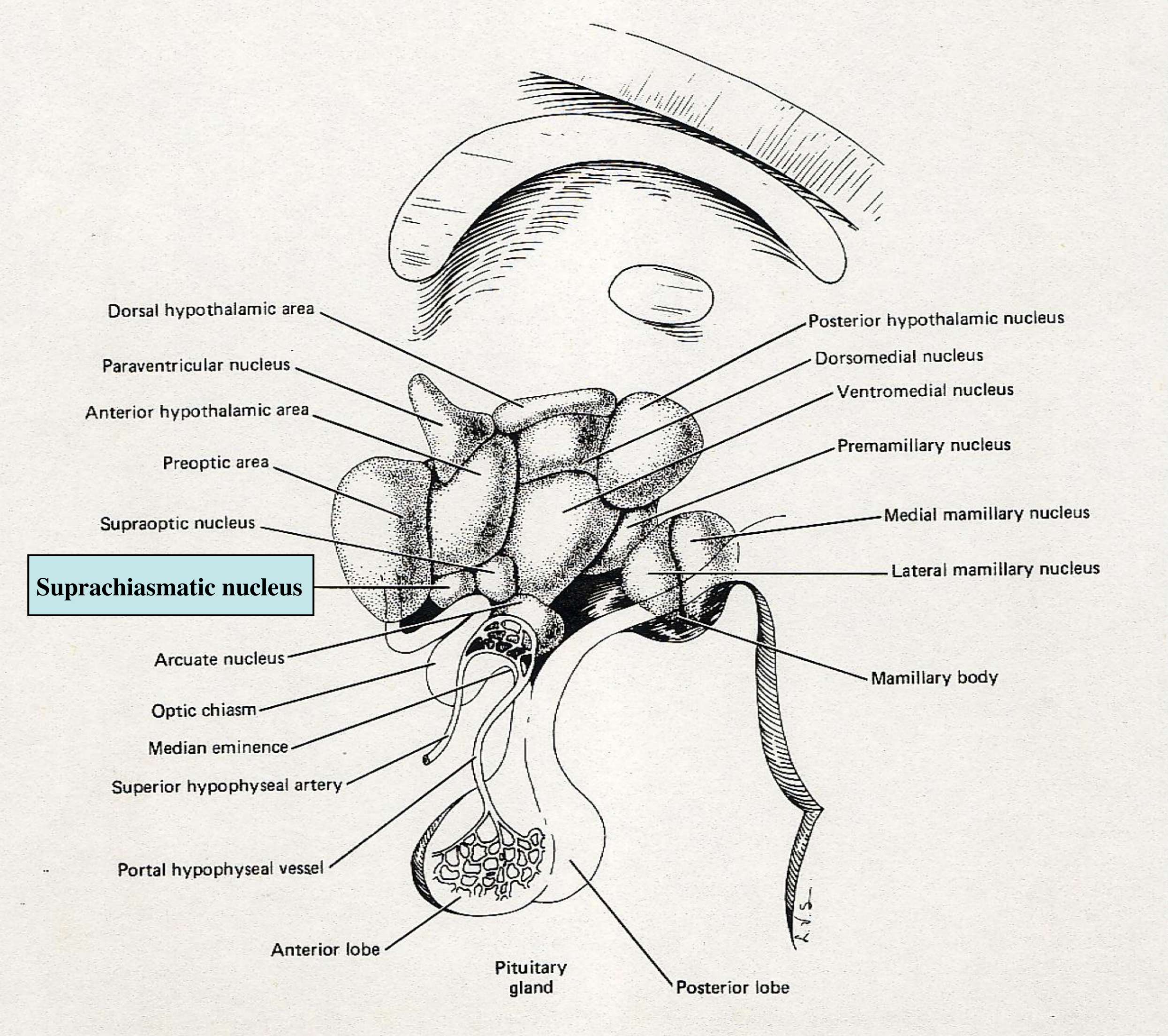
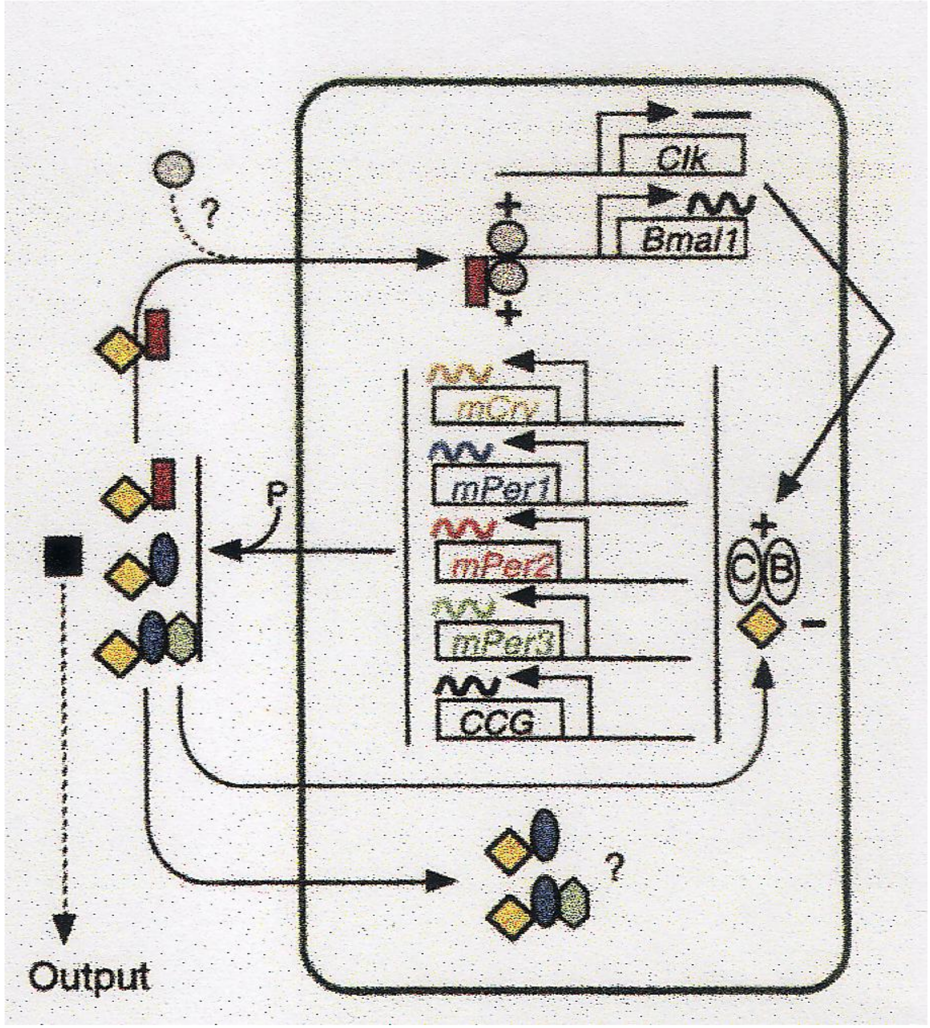


**Figure 3–2.** The human hypothalamus, with a superimposed diagrammatic representation of the portal hypophyseal vessels. (Reproduced, with permission, from Ganong WF: *Review of Medical Physiology,* 12th ed. Lange, 1985.)

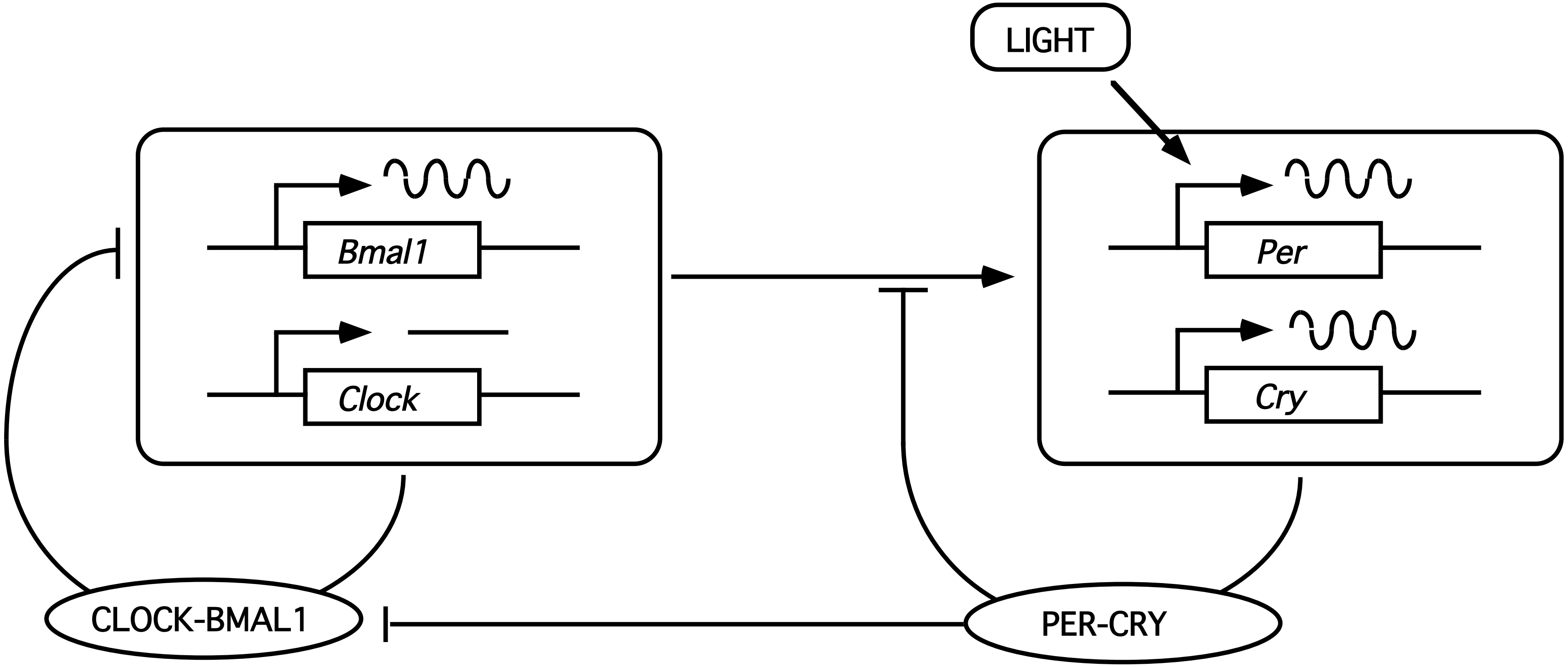
**Shearman LP, Sriram S, Weaver DR, Maywood ES, Chaves I, Zheng B, Kume K, Lee CC, van der Horst GT, Hastings MH & Reppert SM.**

(2000) *Science* **288**:1013-9.

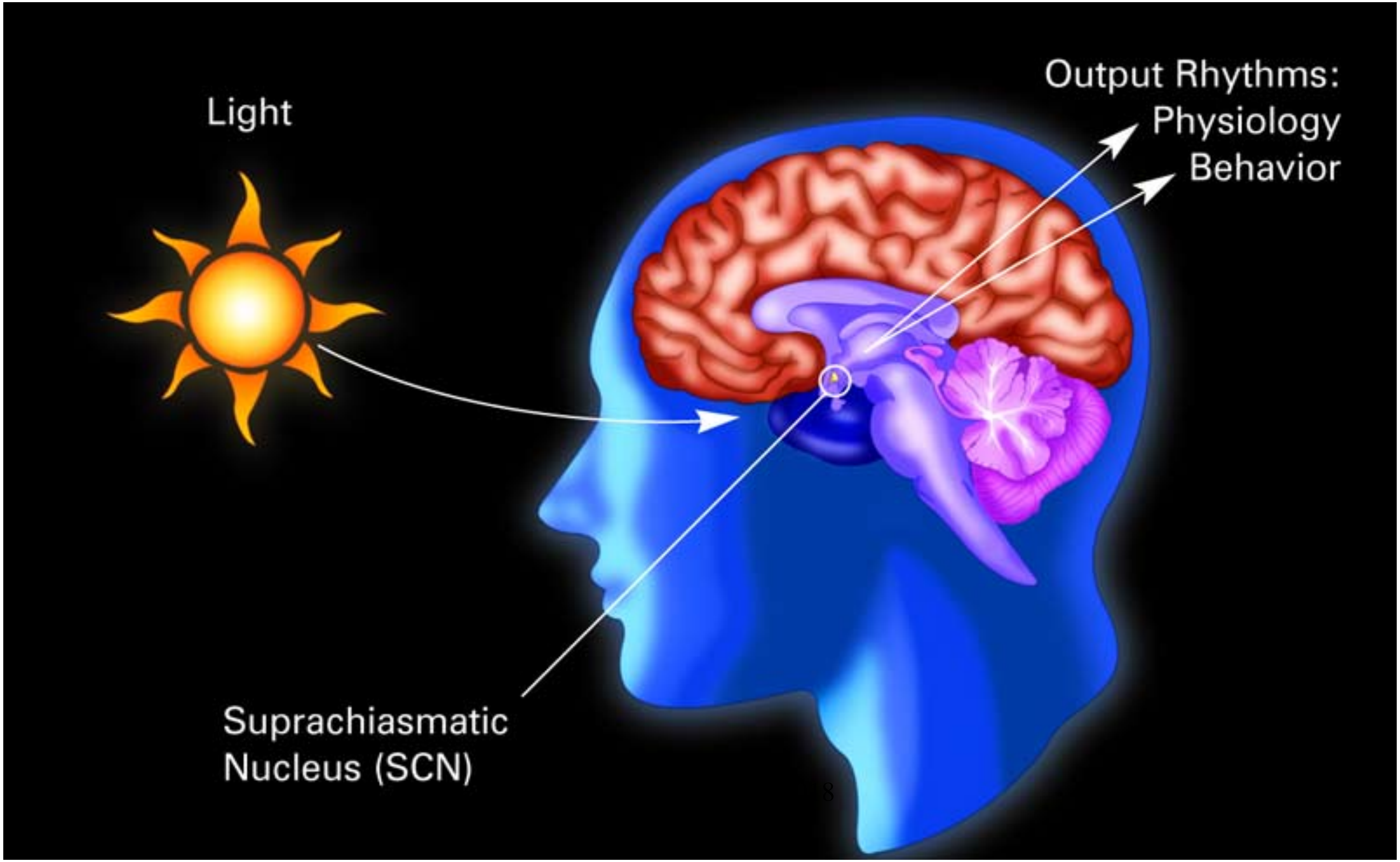
**Interacting molecular loops in the mammalian circadian clock.**

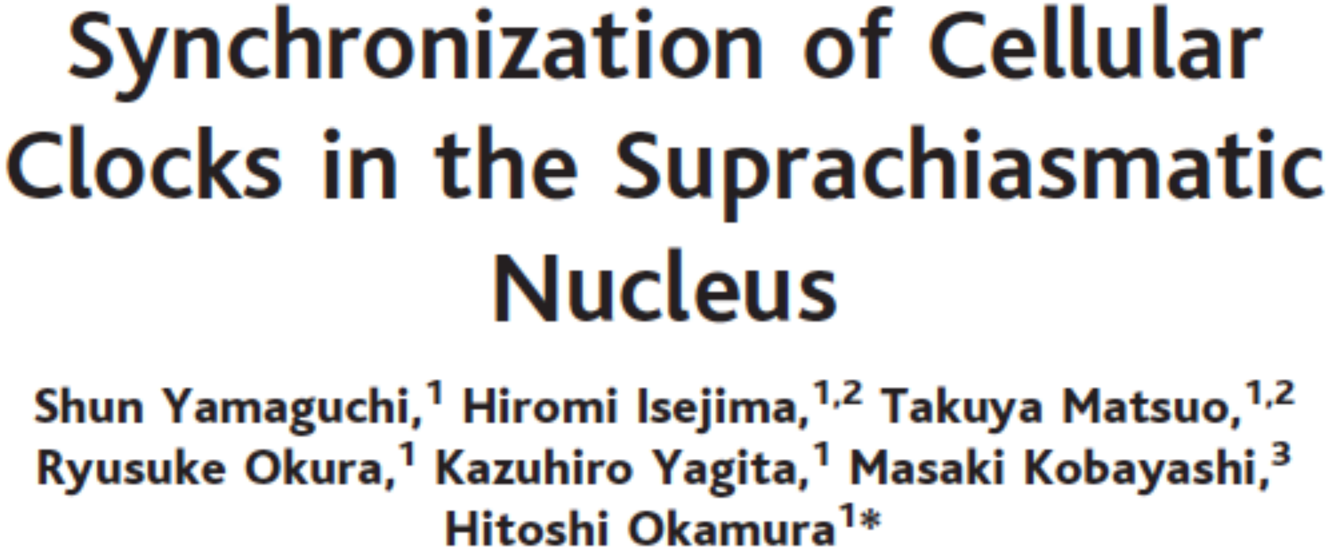


# The mammalian circadian network



# Light, suprachiasmatic nuclei and the circadian clock





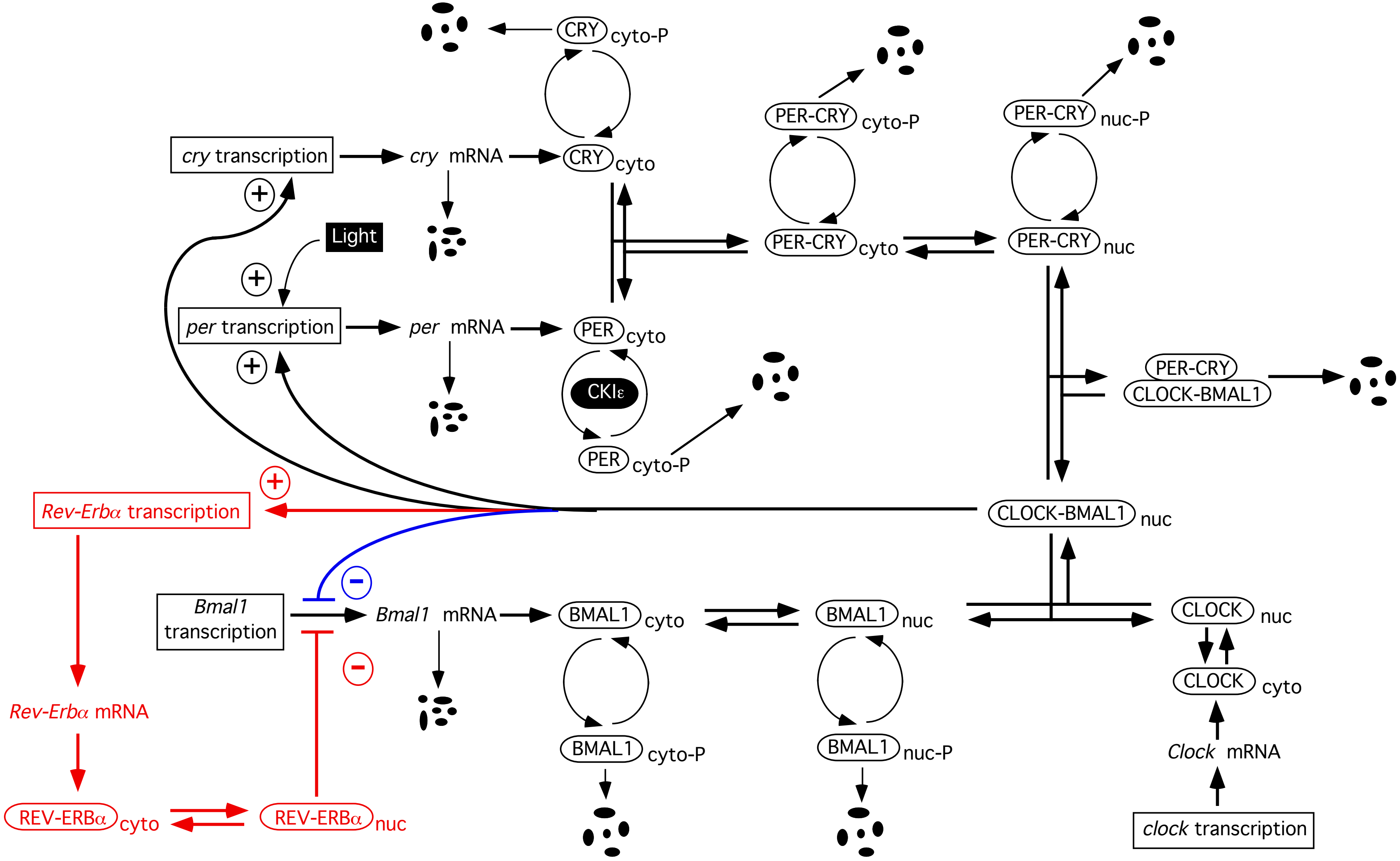
# Synchronization of Cellular Clocks in the Suprachiasmatic Nucleus

**Shun Yamaguchi,[1] Hiromi Isejima,[1,2] Takuya Matsuo,[1,2]**
**Ryusuke Okura,[1] Kazuhiro Yagita,[1] Masaki Kobayashi,[3]**
**Hitoshi Okamura[1]***

*See movie in Supporting Information*

*Science* 302, 1408 (2003)

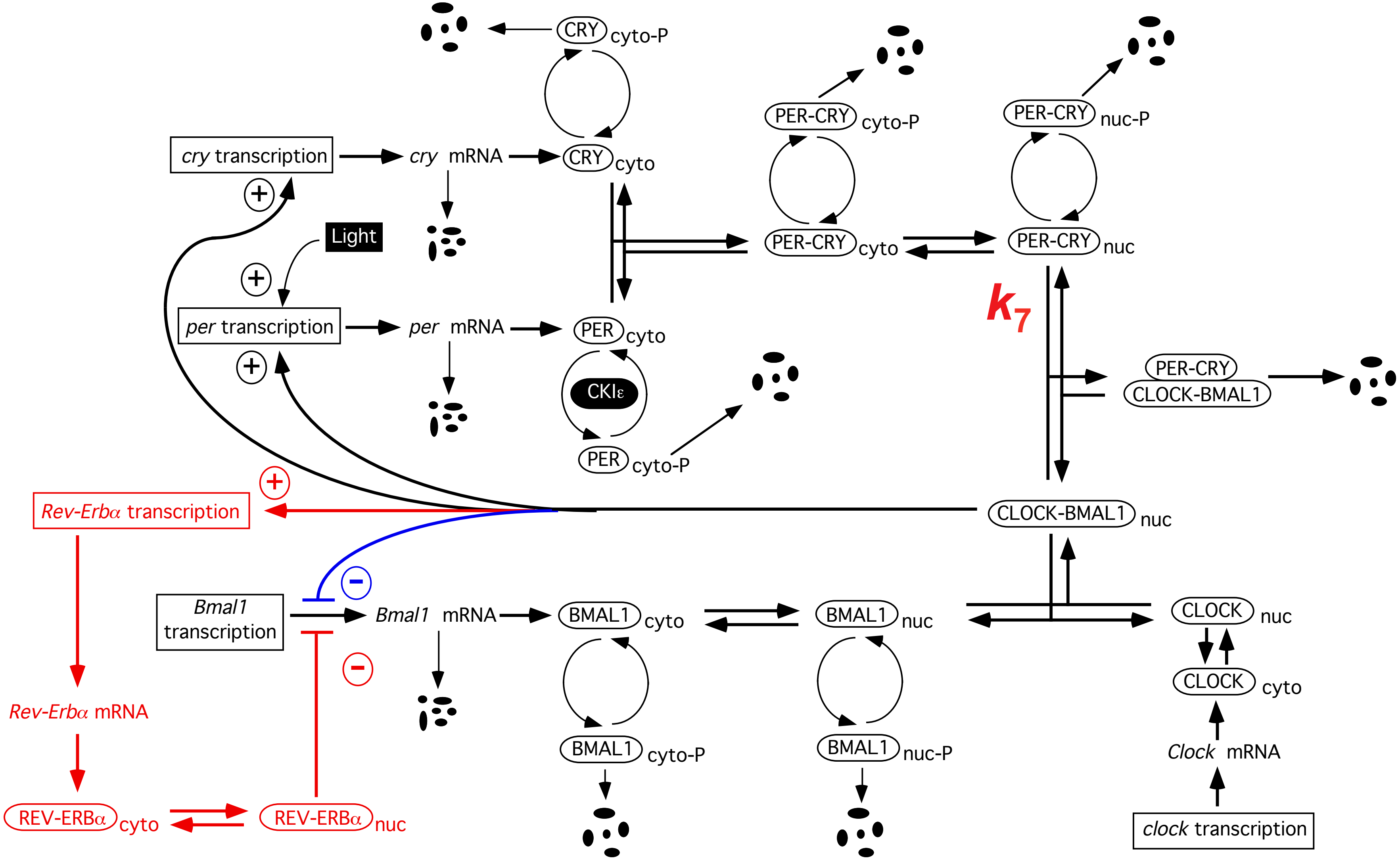
# Model #3 : Model for the mammalian circadian clock



A. Goldbeter-ICTS 2018

J.C. Leloup & A. Goldbeter (2003) *PNAS* 100, 7051-56.

# Model for the mammalian circadian clock



***Other models : Herzel et al; Forger & Peskin; Doyle et al; Kim & Forger***

# Kinetic equations

### a) mRNAs of *Per*, *Cry* and *Bmal1*:

$$\frac{\mathrm{d}M_{\mathrm{P}}}{\mathrm{d}t} = v_{\mathrm{sP}} \frac{B_{\mathrm{N}}^{\mathrm{n}}}{K_{\mathrm{AP}}^{\mathrm{n}} + B_{\mathrm{N}}^{\mathrm{n}}} - v_{\mathrm{mP}} \frac{M_{\mathrm{P}}}{K_{\mathrm{mP}} + M_{\mathrm{P}}} - k_{\mathrm{dn}} M_{\mathrm{P}}$$

$$\frac{\mathrm{d}M_{\mathrm{C}}}{\mathrm{d}t} = v_{\mathrm{sC}} \frac{B_{\mathrm{N}}^{\mathrm{n}}}{K_{\mathrm{AC}}^{\mathrm{n}} + B_{\mathrm{N}}^{\mathrm{n}}} - v_{\mathrm{mC}} \frac{M_{\mathrm{C}}}{K_{\mathrm{mC}} + M_{\mathrm{C}}} - k_{\mathrm{dn}} M_{\mathrm{C}}$$

$$\frac{\mathrm{d}M_{\mathrm{B}}}{\mathrm{d}t} = v_{\mathrm{sB}} \frac{K_{\mathrm{IB}}^{\mathrm{n}}}{K_{\mathrm{IB}}^{\mathrm{n}} + B_{\mathrm{N}}^{\mathrm{n}}} - v_{\mathrm{mB}} \frac{M_{\mathrm{B}}}{K_{\mathrm{mB}} + M_{\mathrm{B}}} - k_{\mathrm{dn}} M_{\mathrm{B}}$$

### c) Phosphorylated and nonphosphorylated PER-CRY complex in cytosol and nucleus:

$$\frac{\mathrm{d}PC_{\mathrm{C}}}{\mathrm{d}t} = -V_{\mathrm{1PC}} \frac{PC_{\mathrm{C}}}{K_{\mathrm{p}} + PC_{\mathrm{C}}} + V_{\mathrm{2PC}} \frac{PC_{\mathrm{CP}}}{K_{\mathrm{dp}} + PC_{\mathrm{CP}}} - k_4 PC_{\mathrm{C}} + k_3 P_{\mathrm{C}} C_{\mathrm{C}} + k_2 PC_{\mathrm{N}} - k_1 PC_{\mathrm{C}} - k_{\mathrm{dn}} PC_{\mathrm{C}}$$

$$\frac{\mathrm{d}PC_{\mathrm{N}}}{\mathrm{d}t} = -V_{\mathrm{3PC}} \frac{PC_{\mathrm{N}}}{K_{\mathrm{p}} + PC_{\mathrm{N}}} + V_{\mathrm{4PC}} \frac{PC_{\mathrm{NP}}}{K_{\mathrm{dp}} + PC_{\mathrm{NP}}} - k_2 PC_{\mathrm{N}} + k_1 PC_{\mathrm{C}} - k_7 B_{\mathrm{N}} PC_{\mathrm{N}} + k_8 I_{\mathrm{N}} - k_{\mathrm{dn}} PC_{\mathrm{N}}$$

$$\frac{\mathrm{d}PC_{\mathrm{CP}}}{\mathrm{d}t} = V_{\mathrm{1PC}} \frac{PC_{\mathrm{C}}}{K_{\mathrm{p}} + PC_{\mathrm{C}}} - V_{\mathrm{2PC}} \frac{PC_{\mathrm{CP}}}{K_{\mathrm{dp}} + PC_{\mathrm{CP}}} - v_{\mathrm{dPCC}} \frac{PC_{\mathrm{CP}}}{K_{\mathrm{d}} + PC_{\mathrm{CP}}} - k_{\mathrm{dn}} PC_{\mathrm{CP}}$$

$$\frac{\mathrm{d}PC_{\mathrm{NP}}}{\mathrm{d}t} = V_{\mathrm{3PC}} \frac{PC_{\mathrm{N}}}{K_{\mathrm{p}} + PC_{\mathrm{N}}} - V_{\mathrm{4PC}} \frac{PC_{\mathrm{NP}}}{K_{\mathrm{dp}} + PC_{\mathrm{NP}}} - v_{\mathrm{dPCN}} \frac{PC_{\mathrm{NP}}}{K_{\mathrm{d}} + PC_{\mathrm{NP}}} - k_{\mathrm{dn}} PC_{\mathrm{NP}}$$

### b) Phosphorylated and nonphosphorylated proteins PER and CRY in the cytosol:

$$\frac{\mathrm{d}P_{\mathrm{C}}}{\mathrm{d}t} = k_{\mathrm{sP}} M_{\mathrm{P}} - V_{\mathrm{1P}} \frac{P_{\mathrm{C}}}{K_{\mathrm{p}} + P_{\mathrm{C}}} + V_{\mathrm{2P}} \frac{P_{\mathrm{CP}}}{K_{\mathrm{dp}} + P_{\mathrm{CP}}} + k_4 PC_C - k_3 P_C C_C - k_{\mathrm{dn}} P_{\mathrm{C}}$$

$$\frac{\mathrm{d}C_{\mathrm{C}}}{\mathrm{d}t} = k_{\mathrm{sC}} M_{\mathrm{C}} - V_{\mathrm{1C}} \frac{C_{\mathrm{C}}}{K_{\mathrm{p}} + C_{\mathrm{C}}} + V_{\mathrm{2C}} \frac{C_{\mathrm{CP}}}{K_{\mathrm{dp}} + C_{\mathrm{CP}}} + k_4 PC_C - k_3 P_C C_C - k_{\mathrm{dn}} C_{\mathrm{C}}$$

$$\frac{\mathrm{d}P_{\mathrm{CP}}}{\mathrm{d}t} = V_{\mathrm{1P}} \frac{P_{\mathrm{C}}}{K_{\mathrm{p}} + P_{\mathrm{C}}} - V_{\mathrm{2P}} \frac{P_{\mathrm{CP}}}{K_{\mathrm{dp}} + P_{\mathrm{CP}}} - v_{dPC} \frac{P_{\mathrm{CP}}}{K_{\mathrm{d}} + P_{\mathrm{CP}}} - k_{\mathrm{dn}} P_{\mathrm{CP}}$$

$$\frac{\mathrm{d}C_{\mathrm{CP}}}{\mathrm{d}t} = V_{\mathrm{1C}} \frac{C_{\mathrm{C}}}{K_{\mathrm{p}} + C_{\mathrm{C}}} - V_{\mathrm{2C}} \frac{C_{\mathrm{CP}}}{K_{\mathrm{dp}} + C_{\mathrm{CP}}} - v_{dCC} \frac{C_{\mathrm{CP}}}{K_{\mathrm{d}} + C_{\mathrm{CP}}} - k_{\mathrm{dn}} C_{\mathrm{CP}}$$

### d) Phosphorylated and nonphosphorylated protein BMAL1 in the cytosol and nucleus:

$$\frac{\mathrm{d}B_{\mathrm{C}}}{\mathrm{d}t} = k_{\mathrm{sB}} M_{\mathrm{B}} - V_{\mathrm{1B}} \frac{B_{\mathrm{C}}}{K_{\mathrm{p}} + B_{\mathrm{C}}} + V_{\mathrm{2B}} \frac{B_{\mathrm{CP}}}{K_{\mathrm{dp}} + B_{\mathrm{CP}}} - k_5 B_C + k_6 B_N - k_{\mathrm{dn}} B_{\mathrm{C}}$$

$$\frac{\mathrm{d}B_{\mathrm{CP}}}{\mathrm{d}t} = V_{\mathrm{1B}} \frac{B_{\mathrm{C}}}{K_{\mathrm{p}} + B_{\mathrm{C}}} - V_{\mathrm{2B}} \frac{B_{\mathrm{CP}}}{K_{\mathrm{dp}} + B_{\mathrm{CP}}} - v_{\mathrm{dBC}} \frac{B_{\mathrm{CP}}}{K_{\mathrm{d}} + B_{\mathrm{CP}}} - k_{\mathrm{dn}} B_{\mathrm{CP}}$$

$$\frac{\mathrm{d}B_{\mathrm{N}}}{\mathrm{d}t} = -V_{\mathrm{3B}} \frac{B_{\mathrm{N}}}{K_{\mathrm{p}} + B_{\mathrm{N}}} + V_{\mathrm{4B}} \frac{B_{\mathrm{NP}}}{K_{\mathrm{dp}} + B_{\mathrm{NP}}} + k_5 B_{\mathrm{C}} - k_6 B_{\mathrm{N}} - k_7 B_{\mathrm{N}} PC_{\mathrm{N}} + k_8 I_{\mathrm{N}} - k_{\mathrm{dn}} B_{\mathrm{N}}$$

$$\frac{\mathrm{d}B_{\mathrm{NP}}}{\mathrm{d}t} = V_{\mathrm{3B}} \frac{B_{\mathrm{N}}}{K_{\mathrm{p}} + B_{\mathrm{N}}} - V_{\mathrm{4B}} \frac{B_{\mathrm{NP}}}{K_{\mathrm{dp}} + B_{\mathrm{NP}}} - v_{\mathrm{dBN}} \frac{B_{\mathrm{NP}}}{K_{\mathrm{d}} + B_{\mathrm{NP}}} - k_{\mathrm{dn}} B_{\mathrm{NP}}$$

### e) Inactive complex between PER-CRY and CLOCK-BMAL1 in nucleus:

$$\frac{\mathrm{d}I_{\mathrm{N}}}{\mathrm{d}t} = -k_8 I_{\mathrm{N}} + k_7 B_N PC_N - v_{\mathrm{dIN}} \frac{I_{\mathrm{N}}}{K_{\mathrm{d}} + I_{\mathrm{N}}} - k_{\mathrm{dn}} I_{\mathrm{N}}$$

*PNAS* (2003)

**Toward a detailed computational model for the mammalian circadian clock.**

**Leloup, JC**, **Goldbeter, A**. 16 or 19 variables

*PNAS* (2003)

**A detailed predictive model of the mammalian circadian clock.**

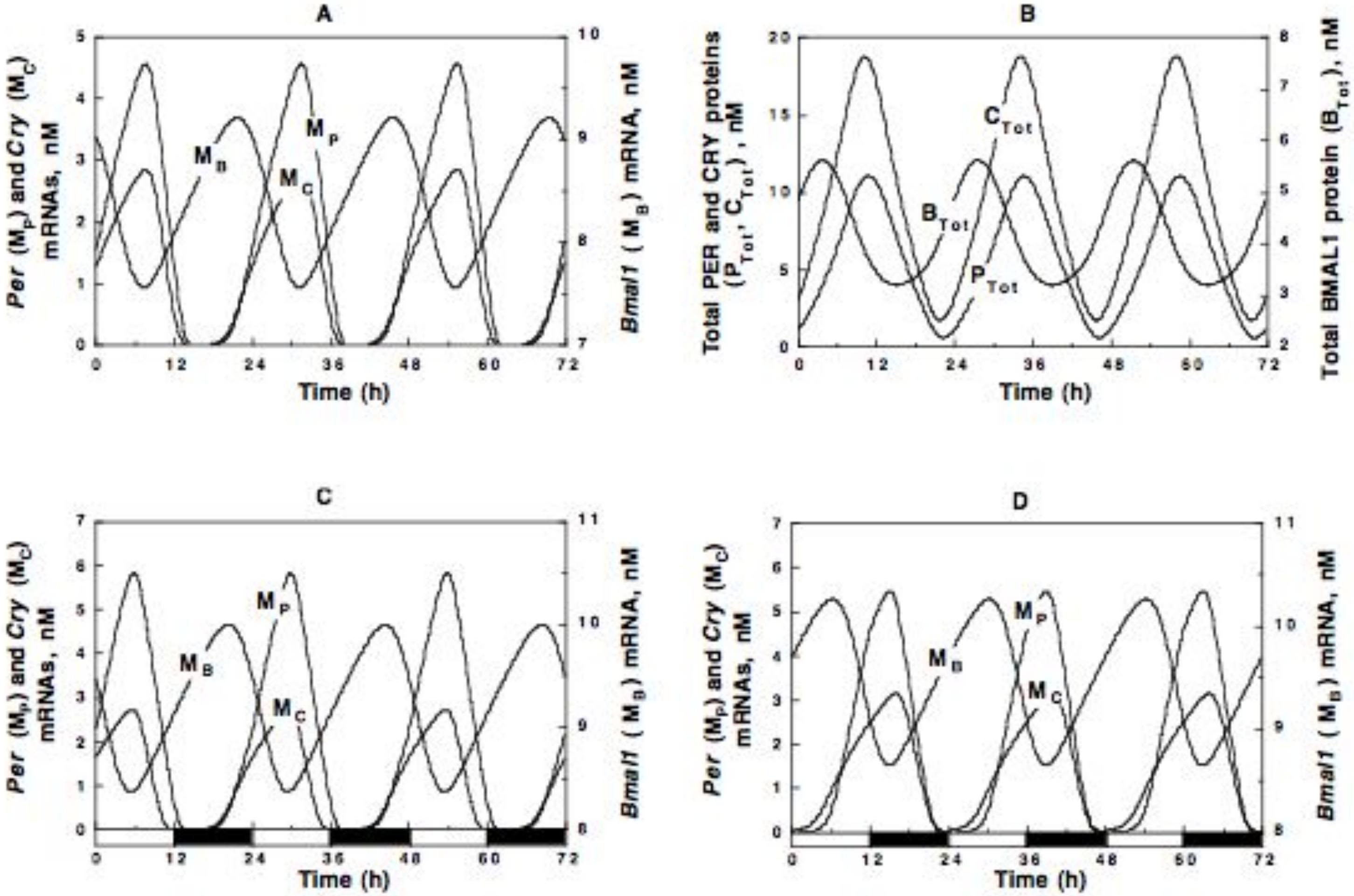
**Forger DB**, **Peskin CS**. 73 variables

*J Biol Rhythms* (2006)

**Development of a two-dimension manifold to represent high dimension mathematical models of the intracellular mammalian circadian clock.**

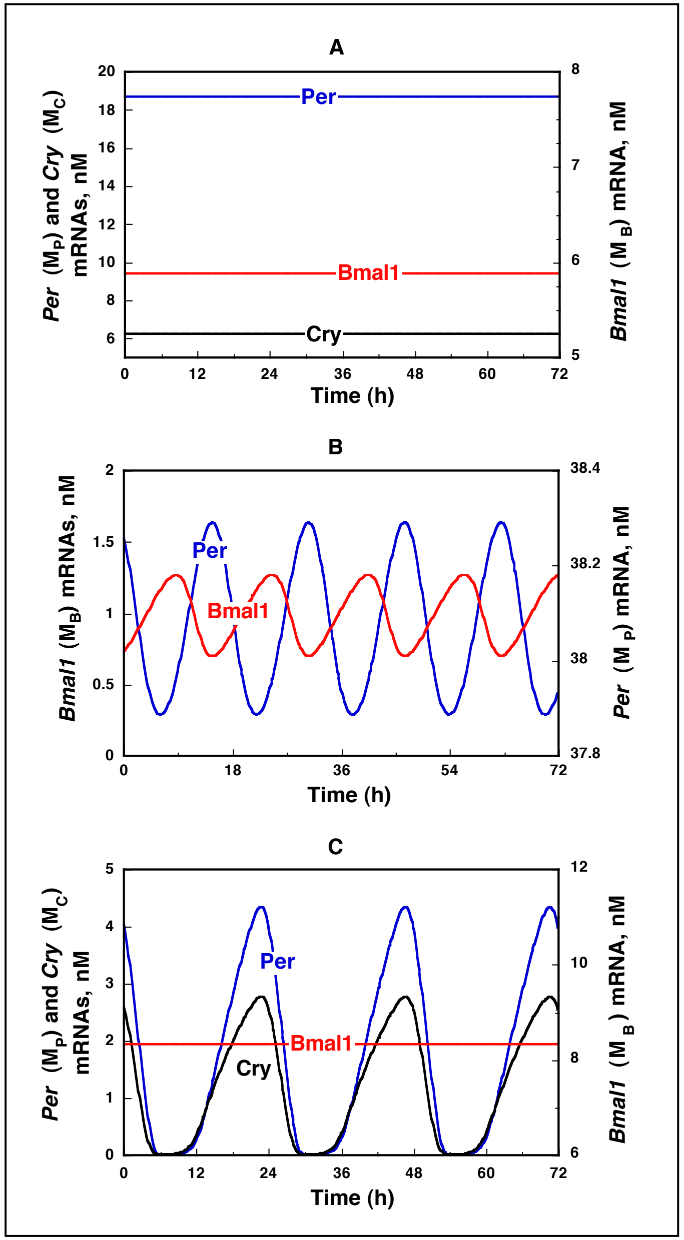
**Indic P**, **Gurdziel K**, **Kronauer RE**, **Klerman EB**.

# Circadian oscillations in continuous darkness and entrainment by light-dark cycles



**DD**

**LD**



*A) No synthesis of PER.*
*Oscillations diosappear*

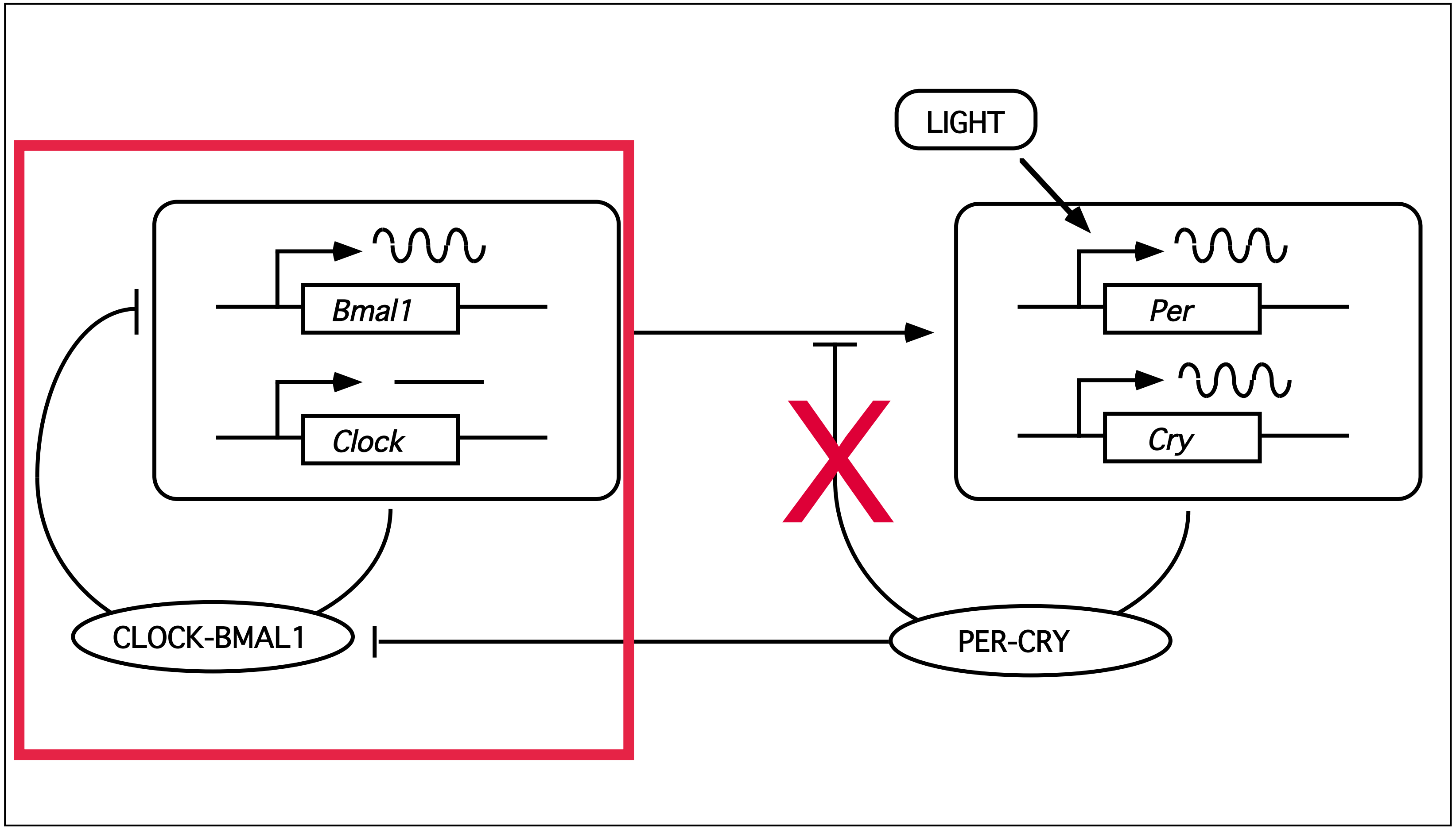
***but***

*B, C) Oscillations can occur in the absence of PER !*

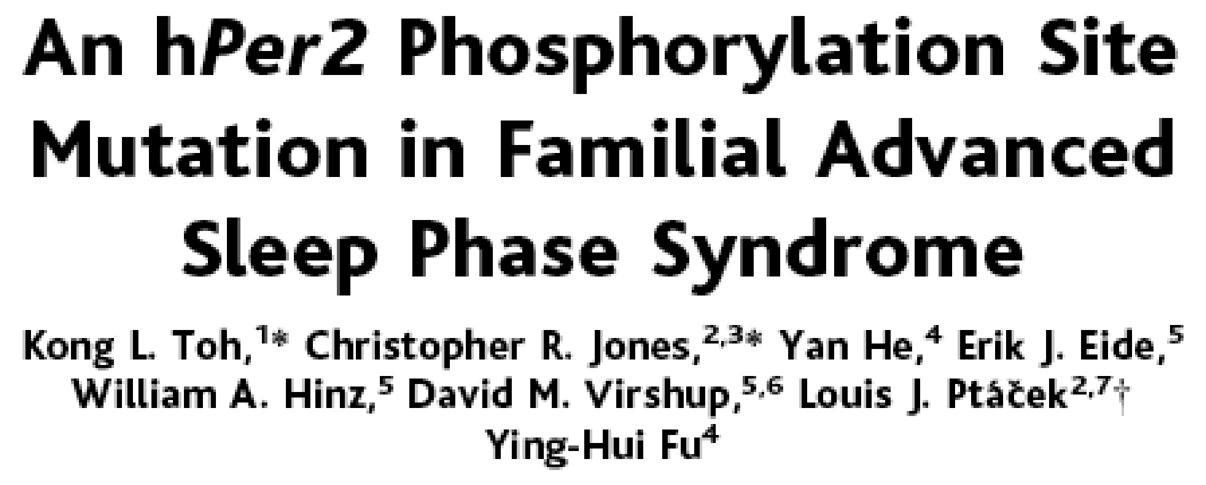
⇨ Multiple sources of oscillations

A. Goldbeter-ICTS 2018

# Model for the mammalian circadian clock: Multiple sources of oscillations



# Link with physiological disorders of the human sleep-wake cycle



# An h*Per2* Phosphorylation Site Mutation in Familial Advanced Sleep Phase Syndrome

Kong L. Toh,[1]* Christopher R. Jones,[2,3]* Yan He,[4] Erik J. Eide,[5]
William A. Hinz,[5] David M. Virshup,[5,6] Louis J. Ptáček[2,7]†
Ying-Hui Fu[4]

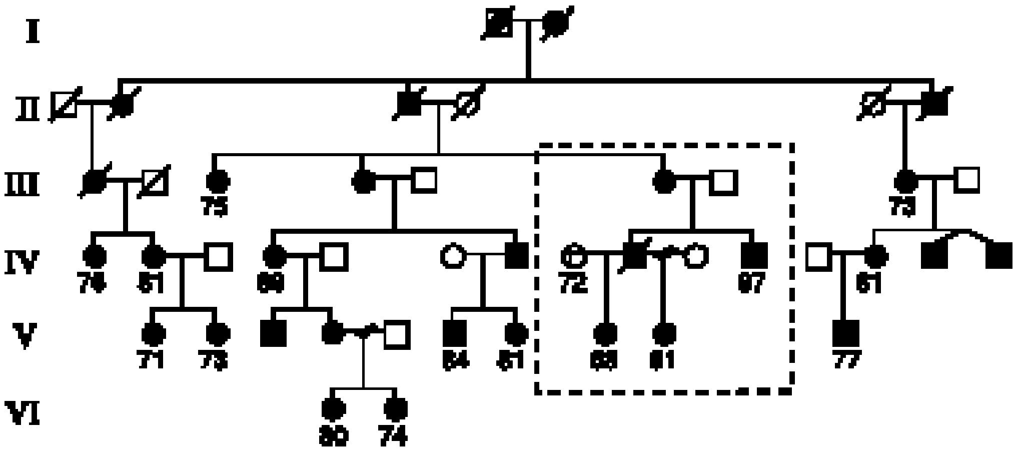
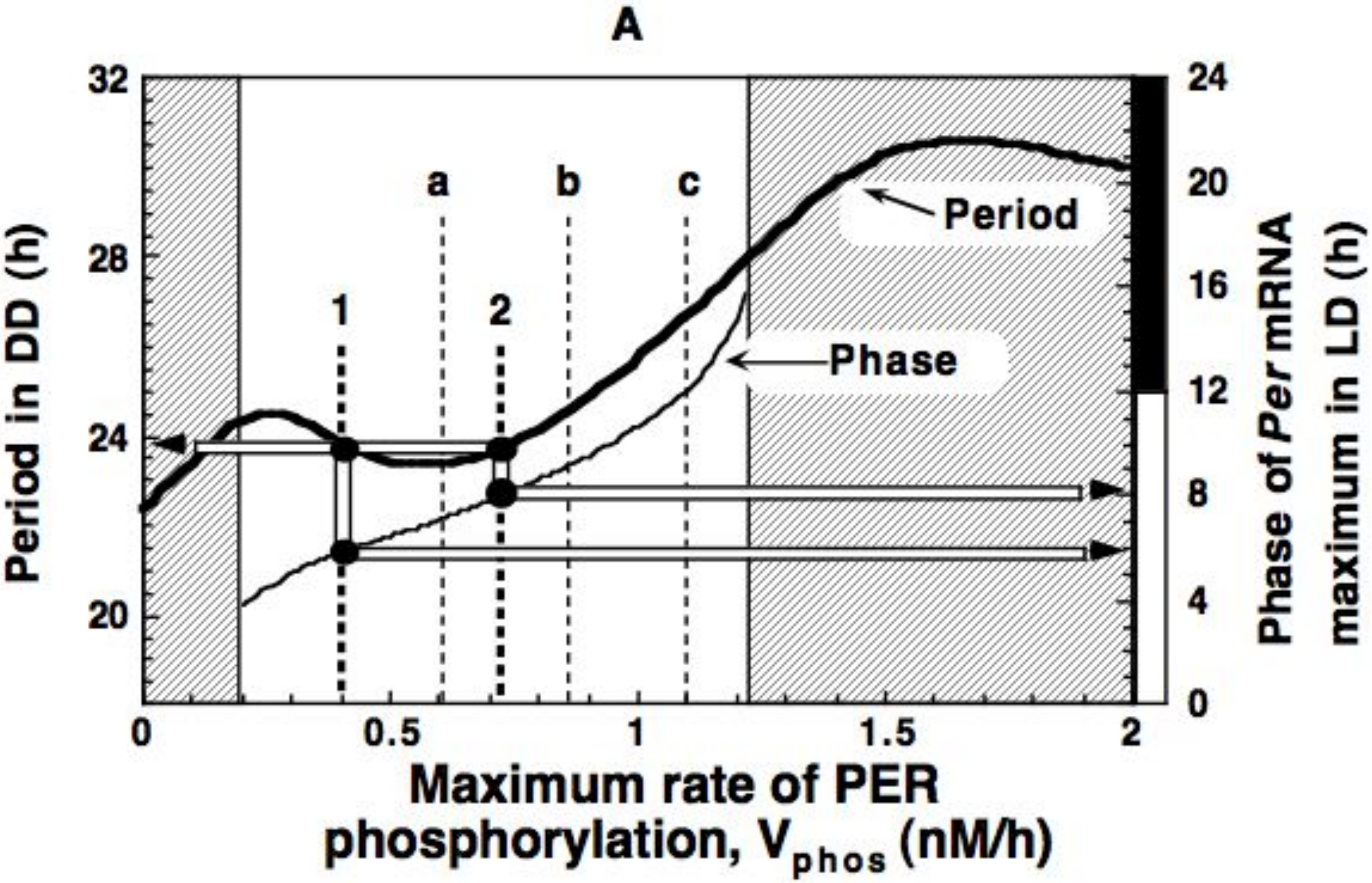


**Fig. 1.** ASPS kindred 2174. Horne-Östberg scores are shown below individuals. The dotted line marks a branch (branch 3) where the ASPS phenotype does not cosegregate with the mutation. Circles, women; squares, men; filled circles and squares, affected individuals; empty circles and squares, unaffected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

*Science* 291, 1040-1043 (2001)

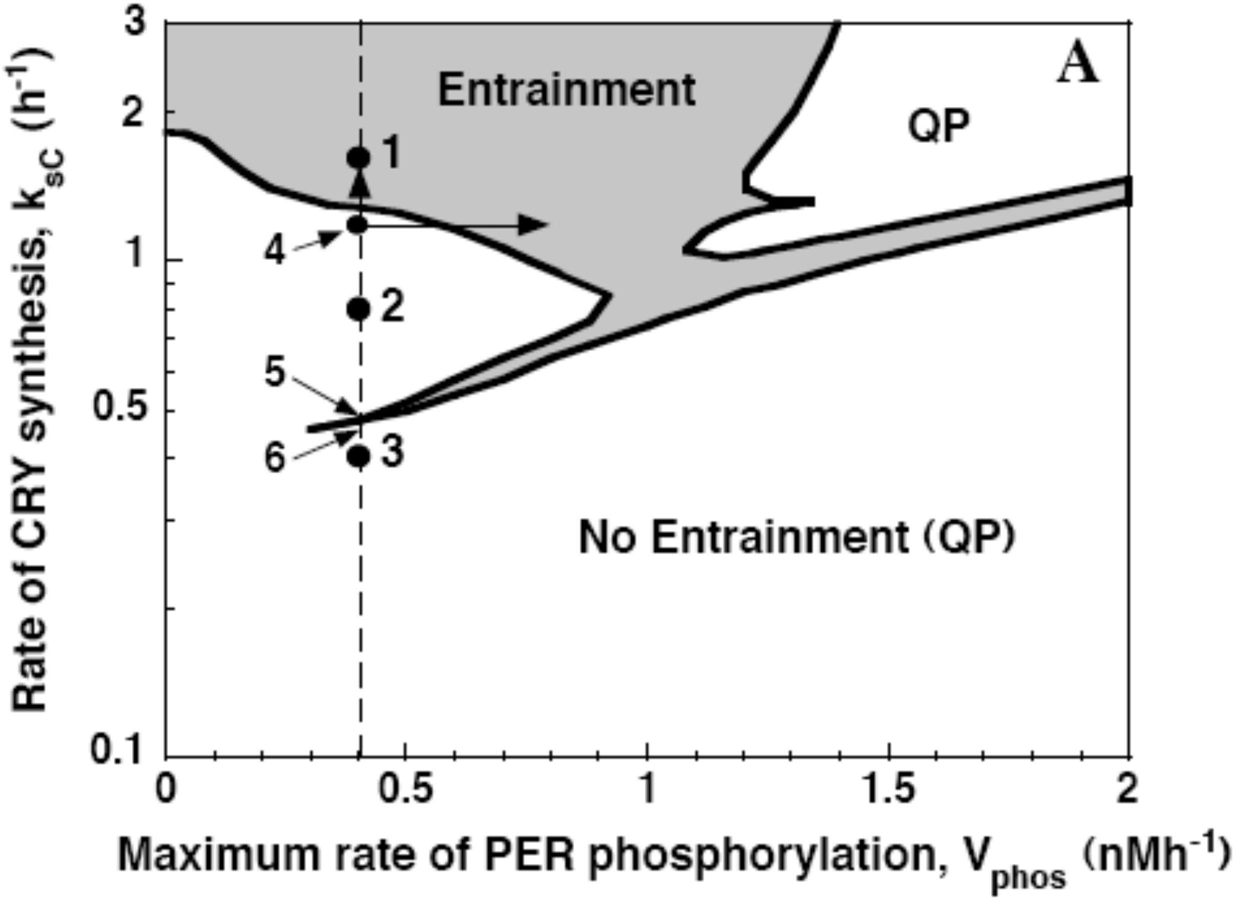

A
Period in DD (h)
32
28
24
20
0
0.5
1
1.5
2
Maximum rate of PER phosphorylation, $V_{phos}$ (nM/h)
Phase of *Per* mRNA maximum in LD (h)
24
20
16
12
8
4
0
a
b
c
1
2
Period
Phase

# Sometimes, entrainment fails to occur…

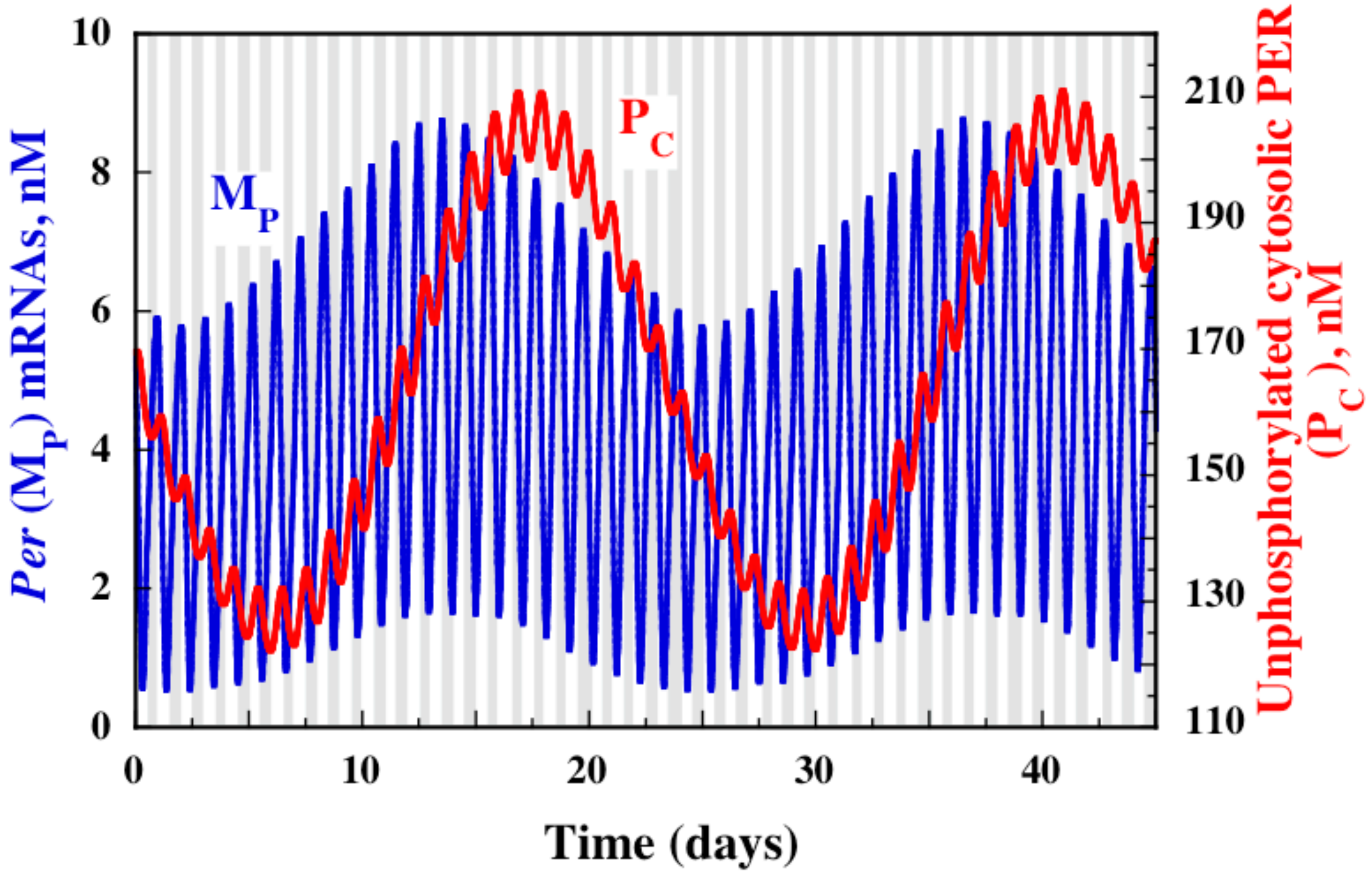
**Simulations helped to identify one possible cause :**

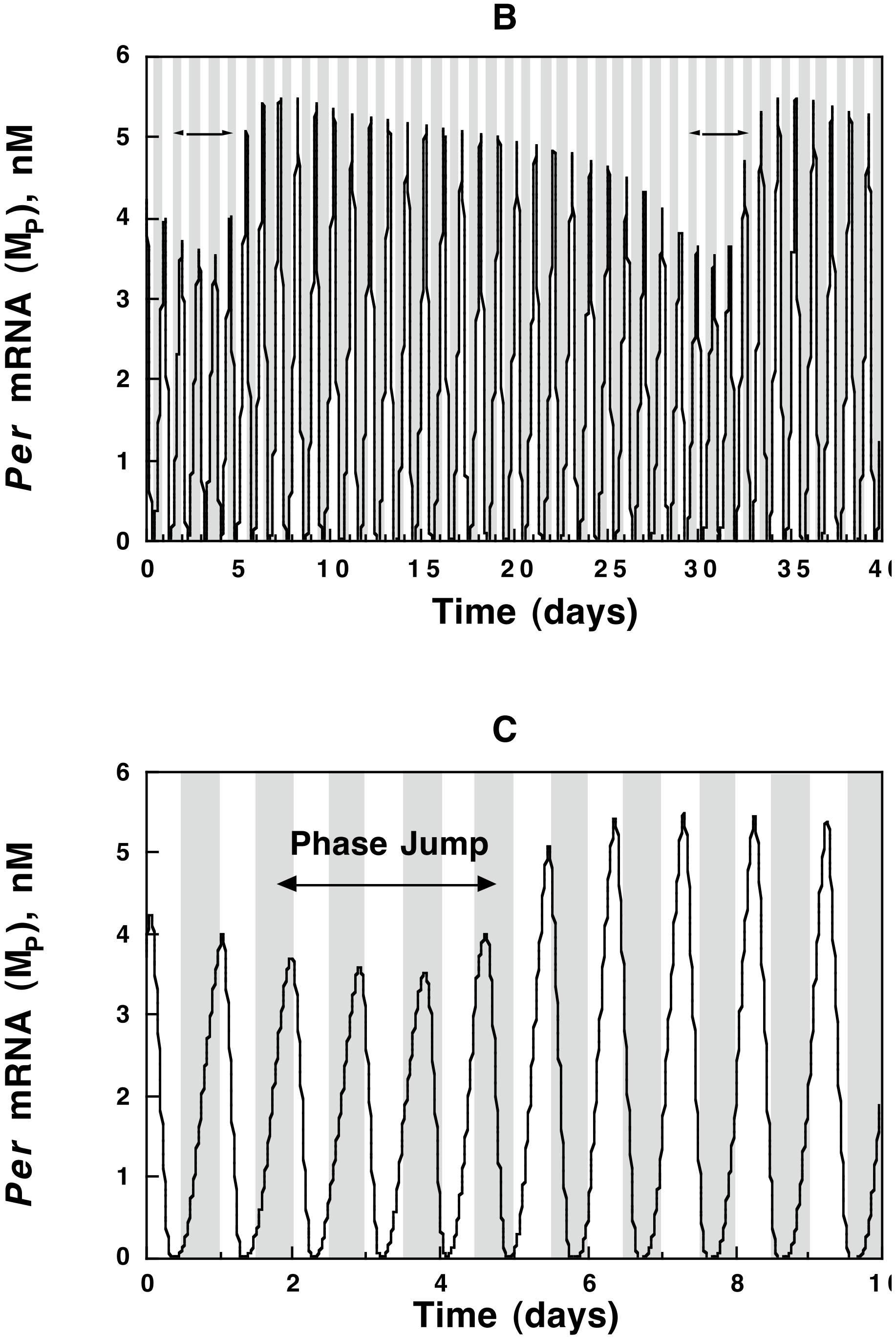
***Levels of CRY might be too low***

# Absence of entrainment of circadian rhythms



*Leloup & Goldbeter (2008) BioEssays*


$M_P$
$P_C$
*Per* ($M_P$) mRNAs, nM
Unphosphorylated cytosolic PER ($P_C$), nM
Time (days)
0
2
4
6
8
10
110
130
150
170
190
210
0
10
20
30
40



## Non 24 h sleep-wake syndrome

Sleep (1996) **19,** 637-40

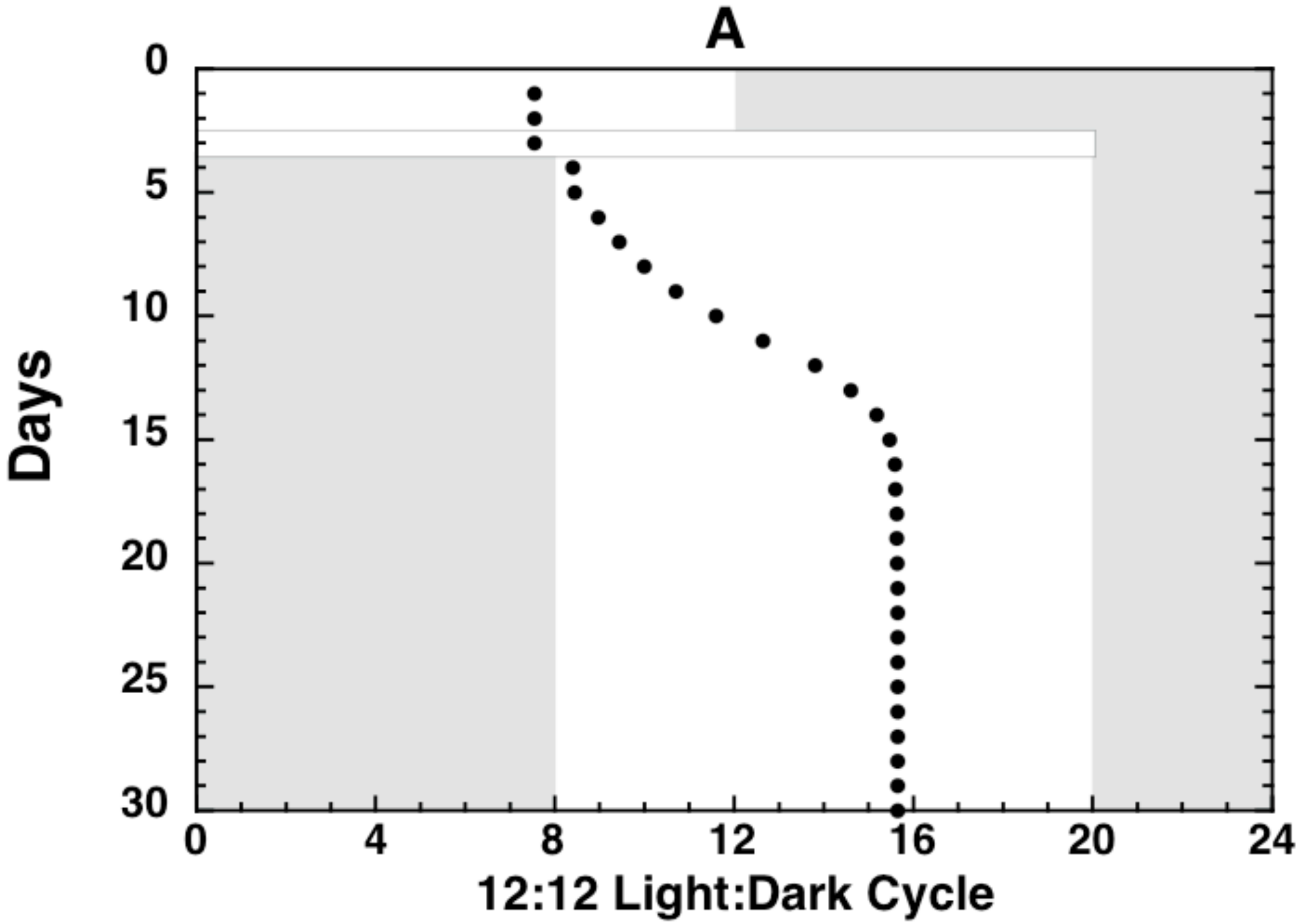
# Delayed phase jumps of sleep onset in a patient with non-24-hour sleep-wake syndrome.

**Uchiyama M, Okawa M, Ozaki S, Shirakawa S, Takahashi K.**
Department of Psychophysiology, National Institute of Mental Health, National Center of Neurology and Psychiatry, Ichikawa, Japan.

We studied a 30-year-old man with non-24-hour sleep-wake syndrome. To investigate the relationship between environmental light-dark cycles and his sleep-wake rhythm, we documented his sleep log and rectal temperature data without any therapeutic interventions. We found that 1) the patient's sleep-wake pattern consisted of two different components, appearing alternatively, with a period of 27.2 days: regular free-run (R free-run), consisting of a daily 30- to 60-minute regular delay of sleep onset; and jumping free-run (J free-run), with clusters of delayed (> 4 hours) phase jumps in sleep onset (DP jump): 2) the frequency of sleep onset was higher during late evening hours to midnight hours than in the daytime; 3) DP jumps occurred exclusively when the prior sleep onset was delayed into the daytime; and 4) a cluster of DP jumps was likely to start when the patient's low temperature zone (a period in which rectal temperature was below average) at subjective night was illuminated by sunlight. These results suggest that DP jumps in the patient may occur due to illumination of the delay portion of the phase-response curve.

# Jet lag

## Time for resynchronization after phase shift of LD cycle



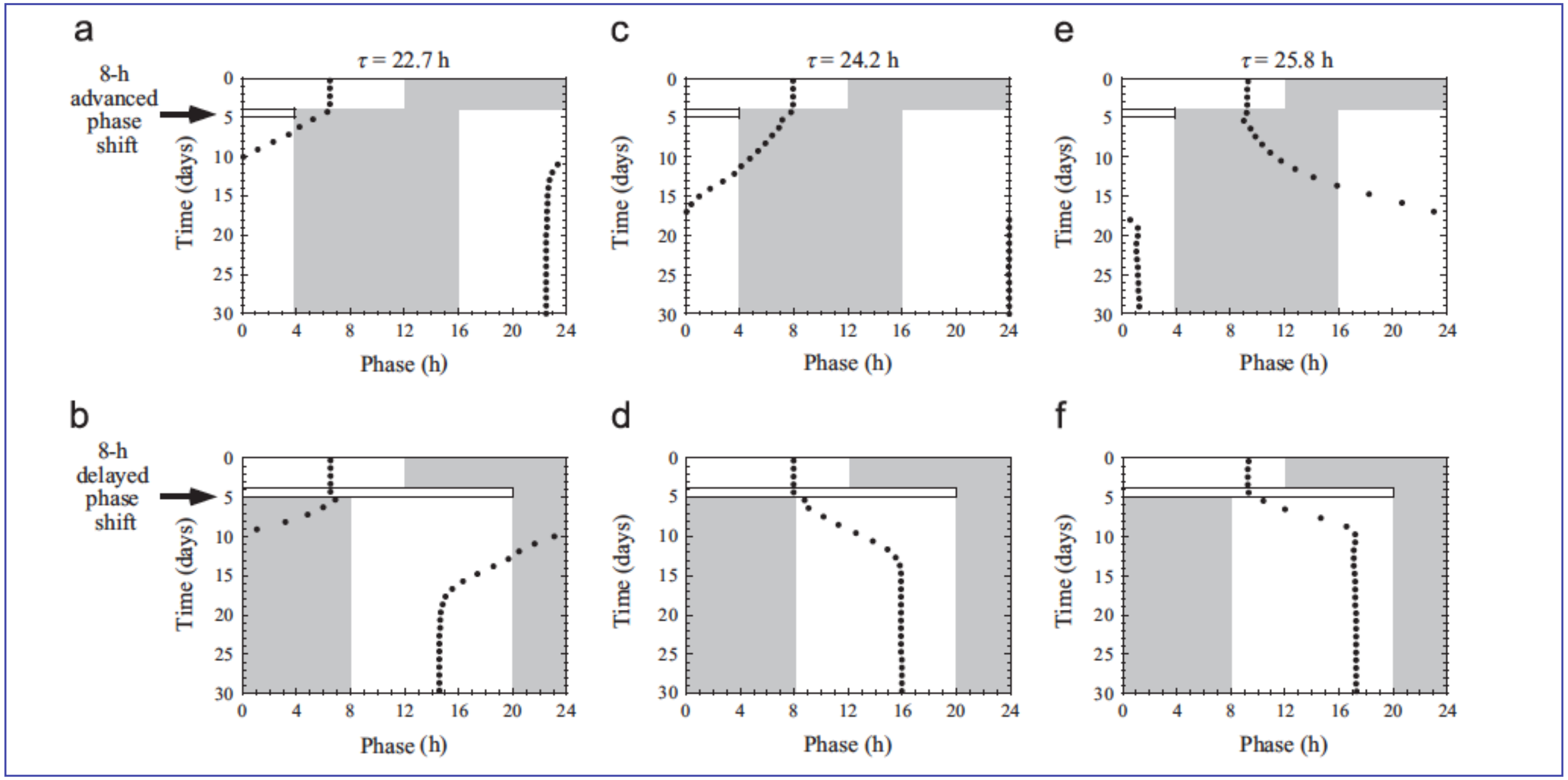
**Delay of 8h**

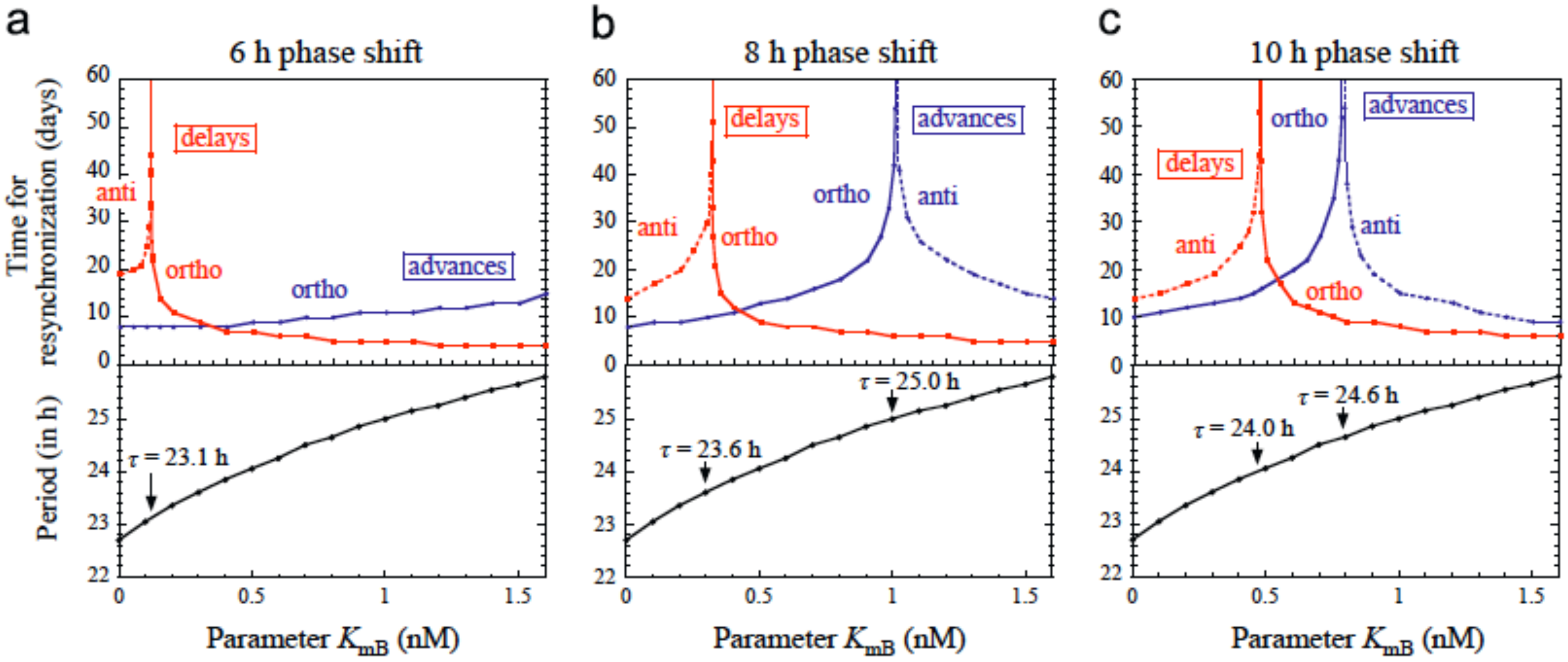
***J. Theor. Biol*. (2013)**

# Critical phase shifts slow down circadian clock recovery: Implications for jet lag

Jean-Christophe Leloup*, Albert Goldbeter

*Faculté des Sciences, Université Libre de Bruxelles, Campus Plaine, C.P. 231, B-1050 Brussels, Belgium*





Leloup & Goldbeter (2013) *J. Theor. Biol.*

# Conclusions

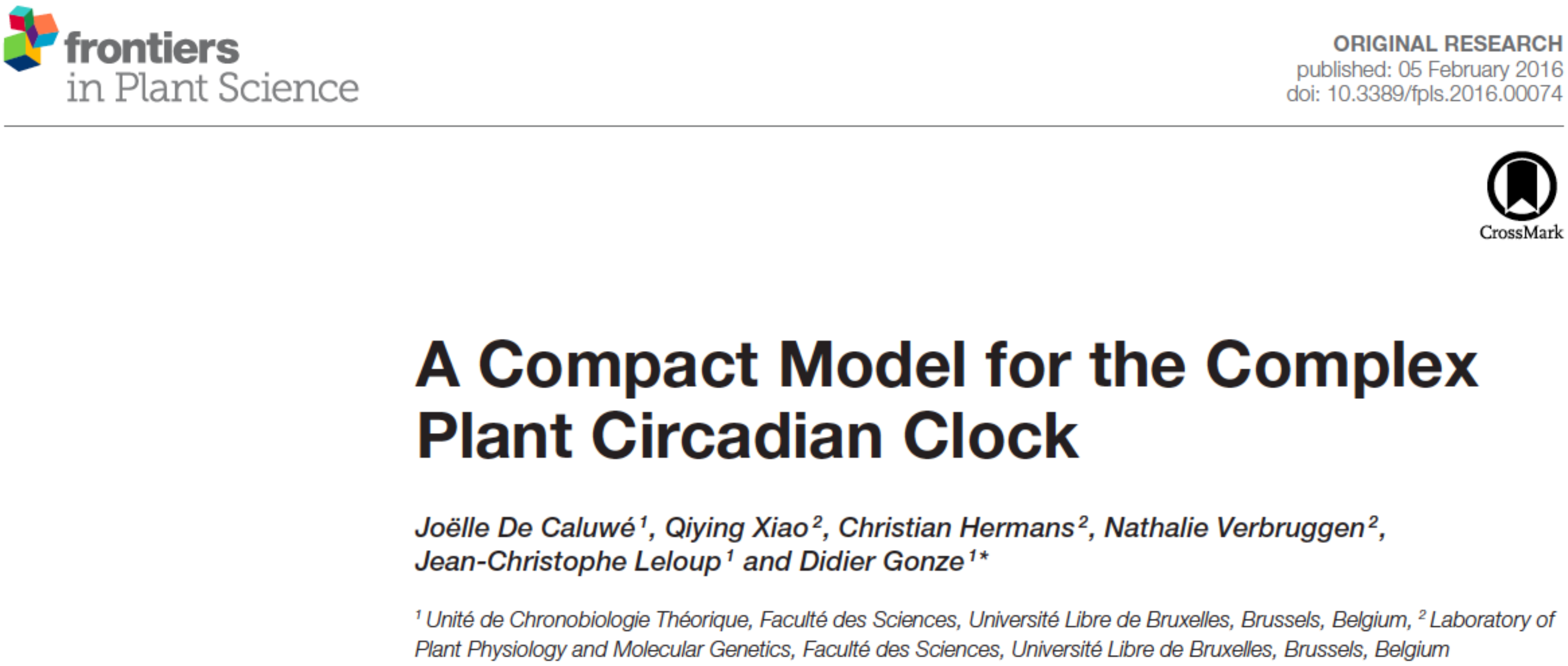
- Circadian rhythms in most organisms —except cyanobacteria— appear to be based on negative autoregulation of gene expression.

- Models of increasing complexity have been proposed for the genetic regulatory network producing circadian rhythms.

- The models (deterministic or stochastic) account for the spontaneous occurrence of circadian rhythms in constant conditions (e.g., continuous darkness).

- The models also account for the entrainment of circadian rhythms by light-dark cycles, and for phase shifts induced by light pulses.

- A model for the mammalian circadian clock can be used to address the dynamical bases of sleep-wake cycle disorders in humans.



frontiers
in Plant Science

ORIGINAL RESEARCH
published: 05 February 2016
doi: 10.3389/fpls.2016.00074

CrossMark

# A Compact Model for the Complex Plant Circadian Clock

*Joëlle De Caluwé [1], Qiying Xiao [2], Christian Hermans [2], Nathalie Verbruggen [2], Jean-Christophe Leloup [1] and Didier Gonze [1]**

*[1] Unité de Chronobiologie Théorique, Faculté des Sciences, Université Libre de Bruxelles, Brussels, Belgium, [2] Laboratory of Plant Physiology and Molecular Genetics, Faculté des Sciences, Université Libre de Bruxelles, Brussels, Belgium*

**9 equations**

*Other models:* Andrew Millar and James Locke

De Caluwé et al.
*Front. Plant Sci.*
(2016)

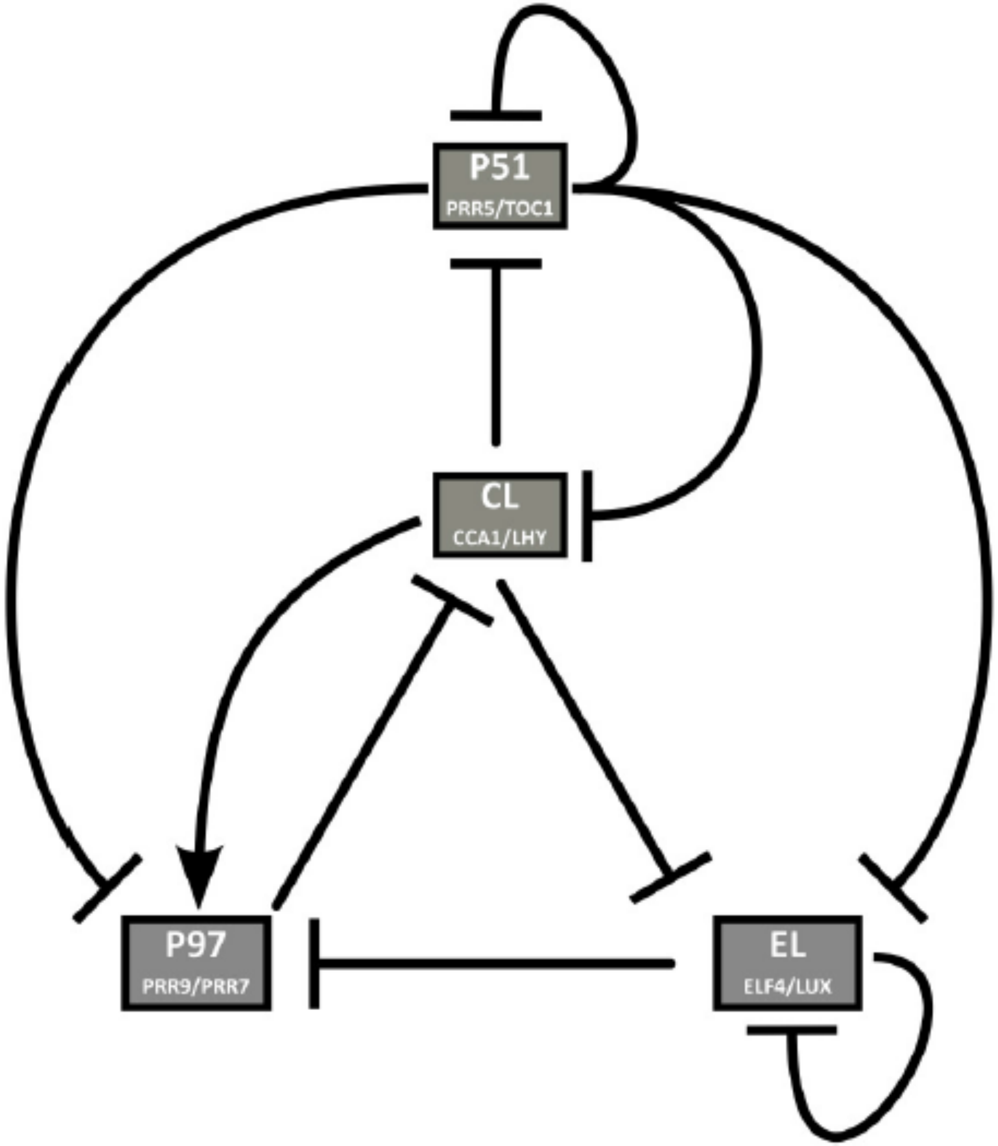


**FIGURE 1 | Clock model structure.** CL represents the dawn genes *CCA1* and *LHY*, P97 represents the morning genes *PRR9* and *PRR7*, P51 represents the evening genes *PRR5* and *TOC1*, and EL represents *ELF4* and *LUX*.

## http://www.ulb.ac.be/sciences/utc

**Jean-Christophe Leloup**

**Didier Gonze**