Circadian rhythms

Biological rhythms

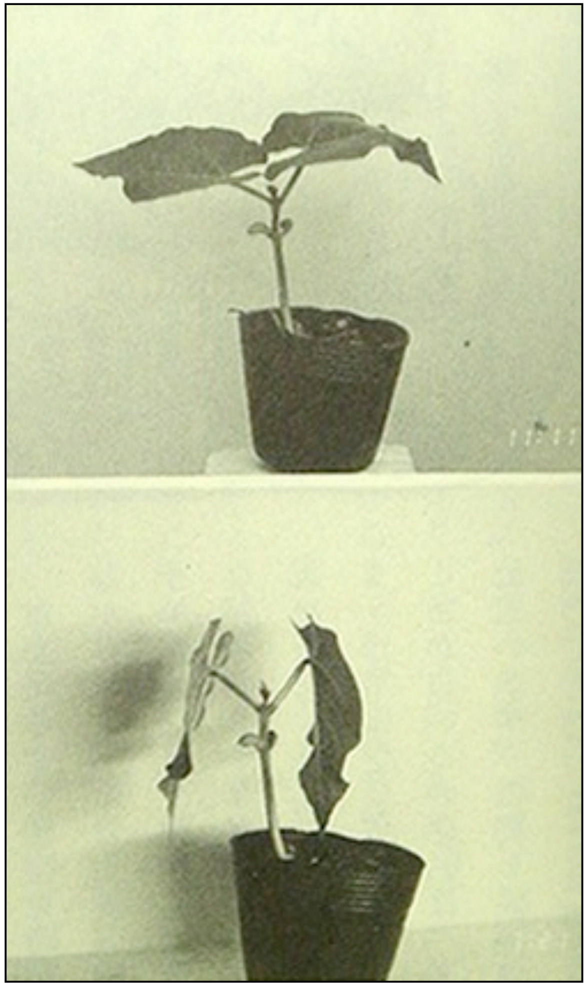
Biological rhythm	Period
Neural rhythms*	0.001 s to 10 s
Cardiac rhythm*	1 s
Calcium oscillations*	sec to min
Biochemical oscillations*	30 s to 20 min
Mitotic oscillator*	10 min to 24 h
Hormonal rhythms*	10 min to 3-5 h (24 h)
Circadian rhythms*	24 h
Ovarian cycle	28 days (human)
Annual rhythms	1 year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

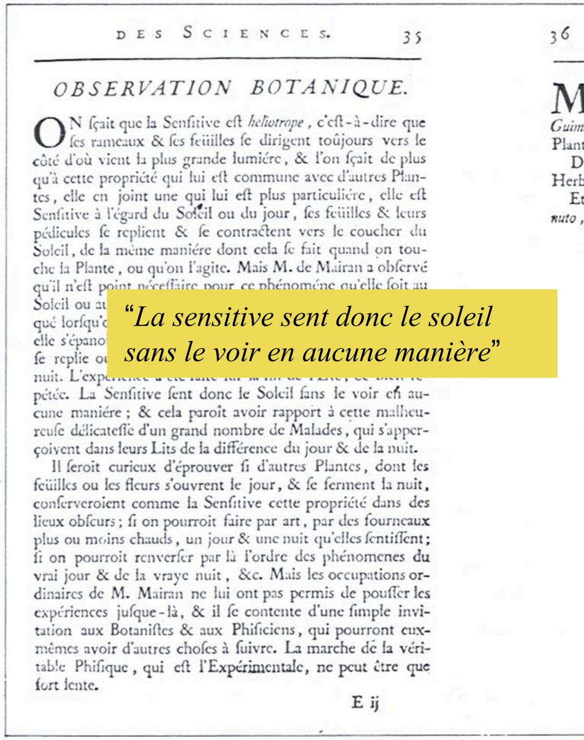
*Cellular rhythms

circadian clocks
(molecular mechanism)

Circadian rhythms

Circadian rhythms are **endogeneous** biological rhythms characterized by a period of **about 24h**...





DES SCIENCES. 35

OBSERVATION BOTANIQUE.

ON ſçait que la Senſitive eſt *heliotrope*, c'eſt-à-dire que ſes rameaux & ſes feüilles ſe dirigent toûjours vers le côté d'où vient la plus grande lumiére, & l'on ſçait de plus qu'à cette propriété qui lui eſt commune avec d'autres Plantes, elle en joint une qui lui eſt plus particuliére, elle eſt Senſitive à l'égard du Soleil ou du jour, ſes feüilles & leurs pédicules ſe replient & ſe contractent vers le coucher du Soleil, de la même maniére dont cela ſe fait quand on touche la Plante, ou qu'on l'agite. Mais M. de Mairan a obſervé qu'il n'eſt point néceſſaire pour ce phénoméne qu'elle ſoit au Soleil ou au [...] qué lorſqu'[...] elle s'épano[...] ſe replie o[...] nuit. L'exp[...] pétée. La Senſitive ſent donc le Soleil ſans le voir en aucune maniére; & cela paroît avoir rapport à cette malheureuſe délicateſſe d'un grand nombre de Malades, qui s'apperçoivent dans leurs Lits de la différence du jour & de la nuit.

Il ſeroit curieux d'éprouver ſi d'autres Plantes, dont les feüilles ou les fleurs s'ouvrent le jour, & ſe ferment la nuit, conſerveroient comme la Senſitive cette propriété dans des lieux obſcurs; ſi on pourroit faire par art, par des fourneaux plus ou moins chauds, un jour & une nuit qu'elles ſentiſſent; ſi on pourroit renverſer par là l'ordre des phénomenes du vrai jour & de la vraye nuit, &c. Mais les occupations ordinaires de M. Mairan ne lui ont pas permis de pouſſer les expériences juſque-là, & il ſe contente d'une ſimple invitation aux Botaniſtes & aux Phiſiciens, qui pourront eux-mêmes avoir d'autres choſes à ſuivre. La marche de la véritable Phiſique, qui eſt l'Expérimentale, ne peut être que fort lente.

E ij

36 HISTOIRE DE L'ACADEMIE ROYALE

M. Marchant a lû la Deſcription

De l'*Althoea* Dioſc. & Plin. C. B. Pin. 315. *Guimauve*, avec la Critique des Auteurs Botaniſtes ſur cette Plante.

De la *Mitella Americana*, *florum foliis fimbriatis*. Inſt. Raii Herb. 242.

Et de la *Sanicula*, ſeu *Cortuſa Americana*, *altera*, *flore minuto*, *fimbriato*. Hort. Reg. Par.

"La sensitive sent donc le soleil sans le voir en aucune manière"

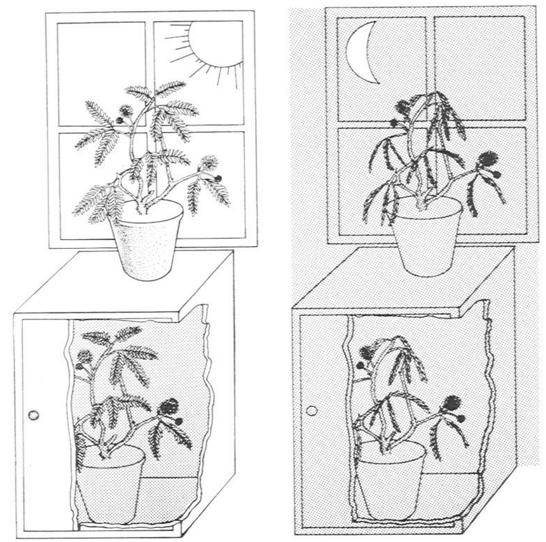
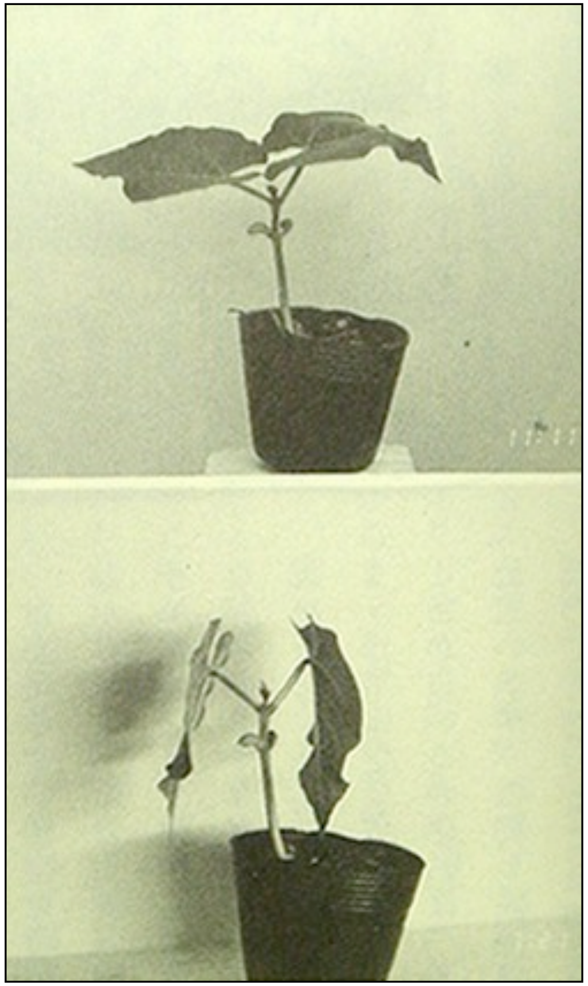


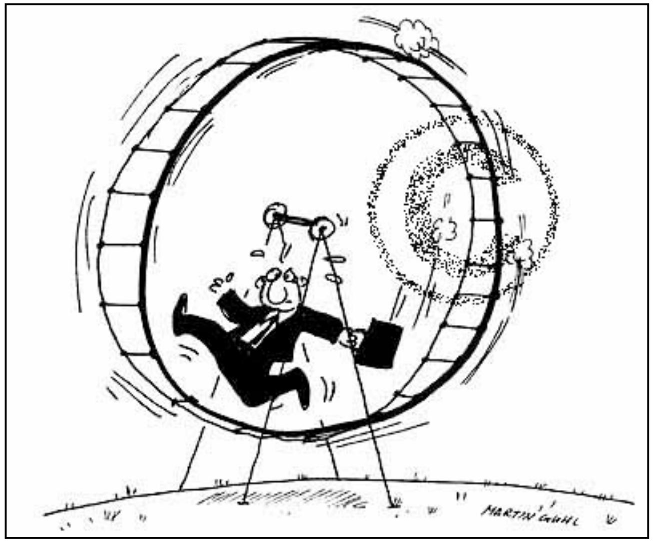
Fig. 1.4 A representation of de Mairan's original experiment. When exposed to sunlight during the day (*upper left*), the leaves of the plant were open, and during the night (*upper right*) the leaves were folded. De Mairan showed that sunlight was not necessary for these leaf movements by placing the plant in total darkness; even under these constant conditions, the leaves opened during the day (*lower left*) and folded during the night (*lower right*). (Copyright 1982 by Moore-Ede, Sulzman, and Fuller.)

Jean-Jacques d'Ortous de Mairan (1740)

Circadian rhythms

Circadian rhythms are **ubiquitous**. They allow living organisms to live in phase with the alternance of day and night...





Circadian rhythms

Our biological clock regulates many physiological functions:

- Blood pressure
- Body temperature
- Hormone secretion
- Sleep-wake cycle
- Heart beat
- Metabolism
- Cell cycle
- Response to drugs
- ...

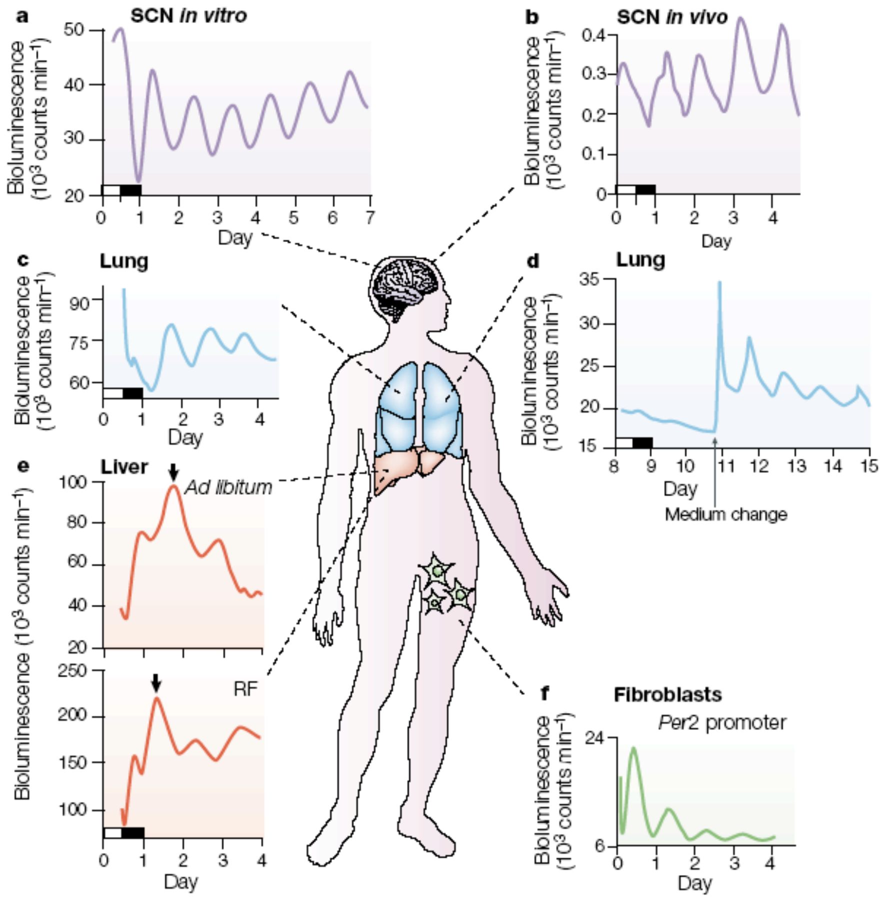
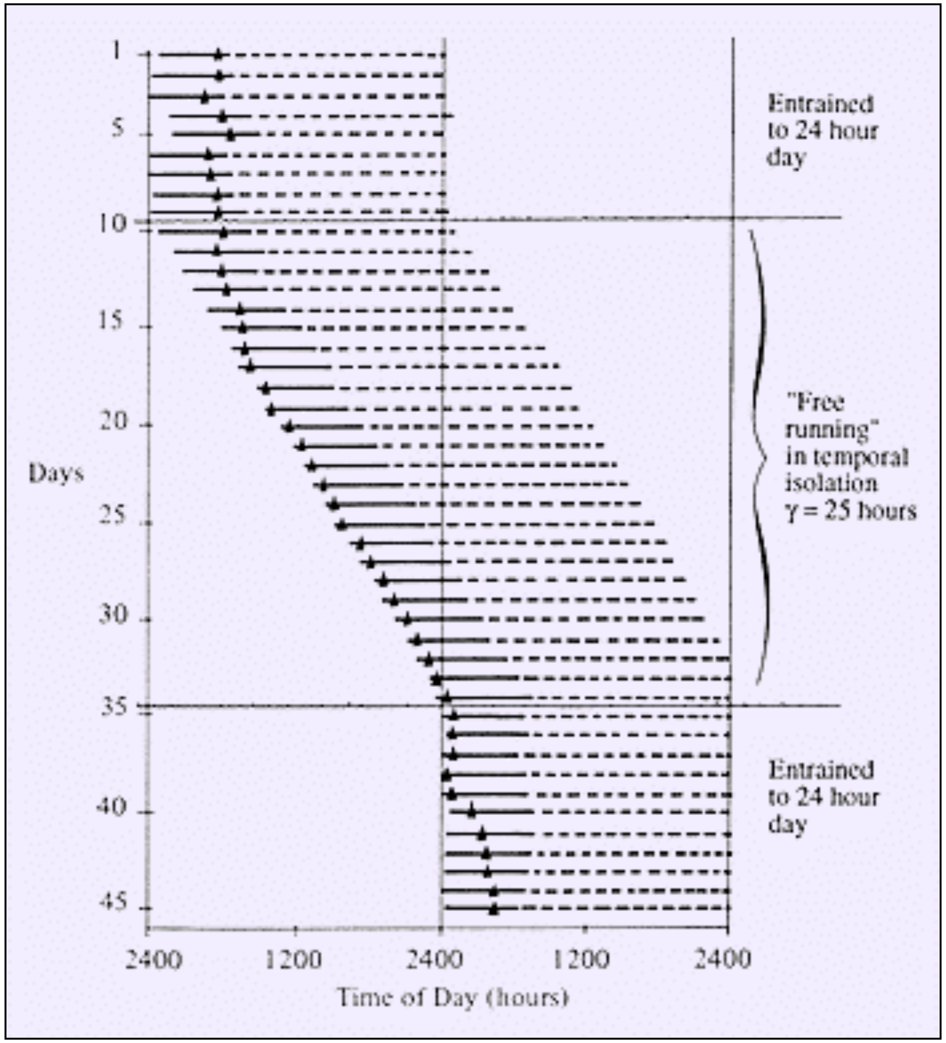


Figure 3 | *Per::luciferase* transgenes reveal a diversity of tissue-based circadian oscillators.

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

Circadian rhythms

Free-run vs entrainment



- In **constant conditions**, the *free-running period* of circadian rhythm is *around* 24h (but not exactly 24h)

Franz Halberg (born in 1919)

Father of Chronobiology

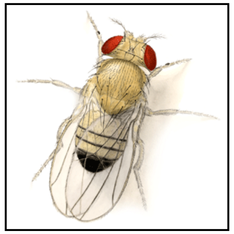
Coined the term *circadian* (1959)

circa (around) dies (day)

- In **natural conditions** circadian rhythms are *entrained* by the external light-dark cycle and the period is *exactly* 24h.

Circadian rhythms

Monitoring the locomotor activity of flies (wild type and perS mutant)



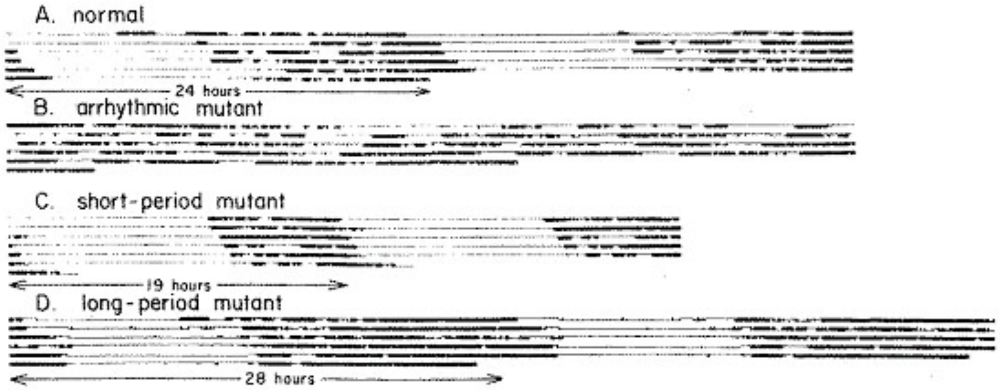
See animations: droso_activity_WT.avi and droso_activity_PERS.avi

HHMI
HOWARD HUGHES MEDICAL INSTITUTE

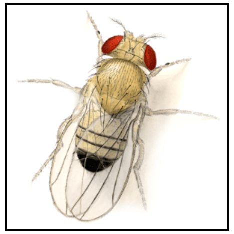
Source: http://www.hhmi.org/biointeractive/clocks/animations.html

Circadian rhythms: genetic bases

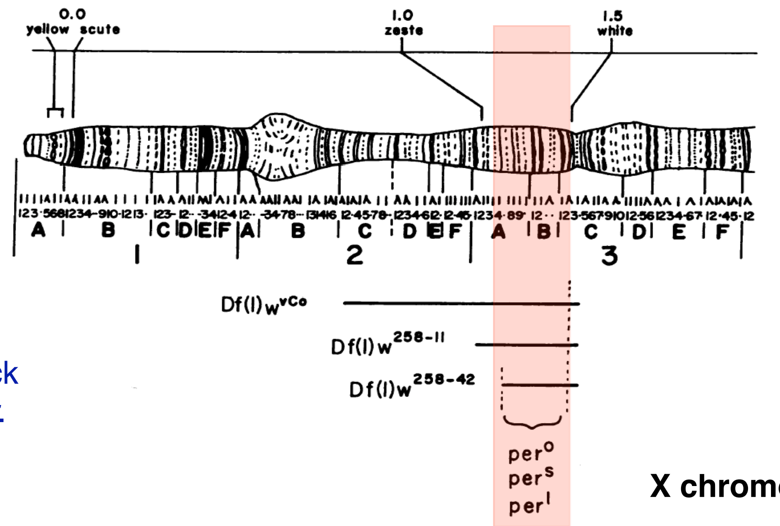
Locomotor activity



Drosophila



Identification of the *period* (*per*) gene



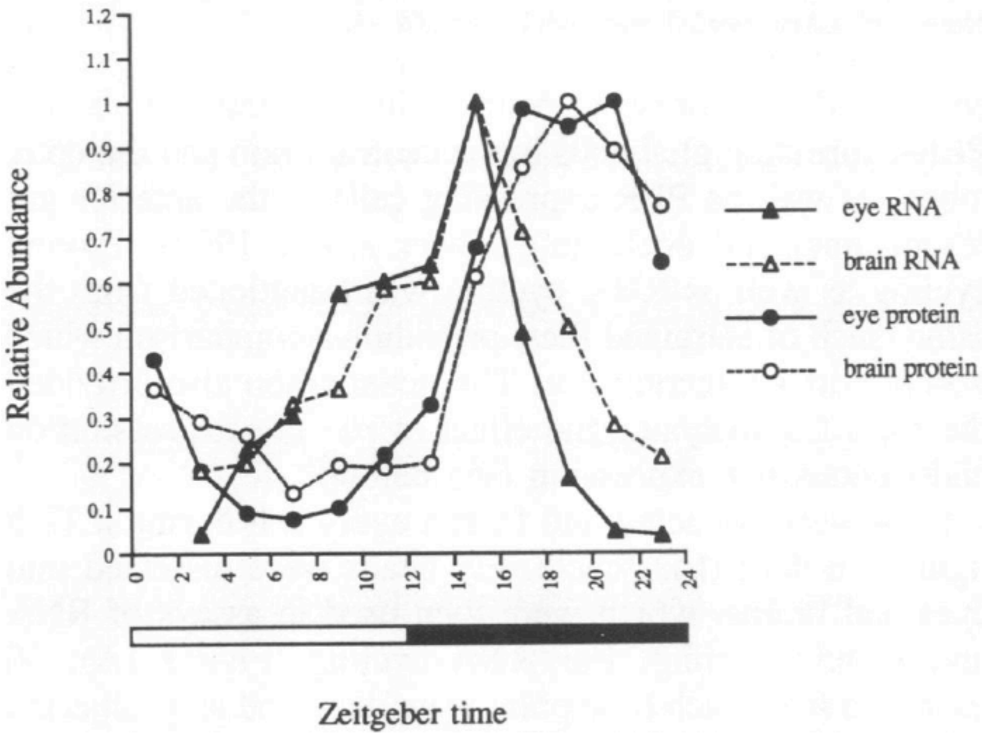
X chromosome

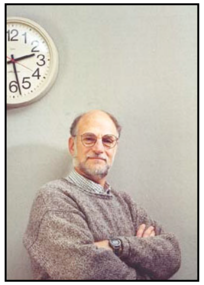
Konopka RJ & Benzer S (1971) Clock mutants of *Drosophila melanogaster*. *Proc Natl Acad Sci USA* 68, 2112-6.

Circadian rhythms: genetic bases

Oscillations of *per* mRNA and PER protein in *Drosophila*

- Levels of *per* mRNA and PER proteins oscillates with a circadian period (both in the eye and in the brain of the fly).
- The peak of PER protein occurs a few hours after the peak of mRNA.
- The fact that mRNA level decreases when the level of protein is high (together with other experiments) suggests that the PER protein inhibits the expression of the *per* gene.

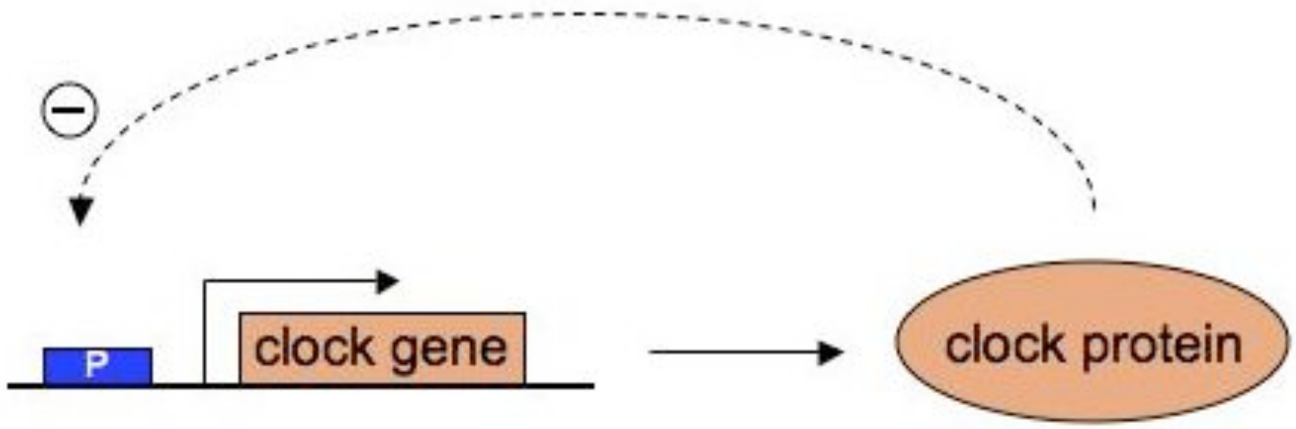




Zeng H, Hardin PE, Rosbash M (1994) Constitutive overexpression of the *Drosophila* period protein inhibits *period* mRNA cycling. *EMBO J.* 13: 3590-3598.

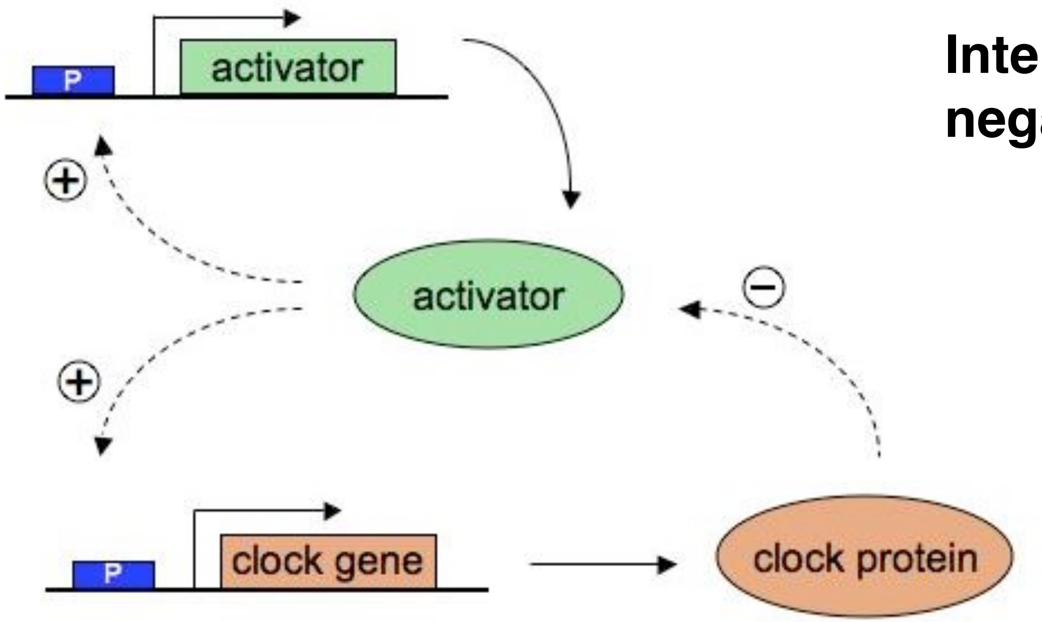
Molecular mechanism of circadian clocks

Core mechanism: negative feedback loop



clock gene	
Drosophila	***per*** *(period),* ***tim*** *(timeless)*
Mammals	***mper1-3*** *(period homologs)*
Neurospora	***frq*** *(frequency)*

Molecular mechanism of circadian clocks



Interlocked positive and negative feedback loops

	Clock gene	Activator	Effect of light
Drosophila	*per, tim*	*clk, cyc*	TIM degradation
Mammals	*mper1-3, cry1,2*	*clock, bmal1*	*per* transcription
Neurospora	*frq*	*wc-1, wc-2*	*frq* transcription

Dunlap JC (1999) Molecular bases for circadian clocks. *Cell* 96: 271-290.
Young MW & Kay SA (2001) Time zones: a comparative genetics of circadian clocks. *Nat. Genet.* 2: 702-715.

Molecular mechanism of circadian clocks

Circadian clock in mammals

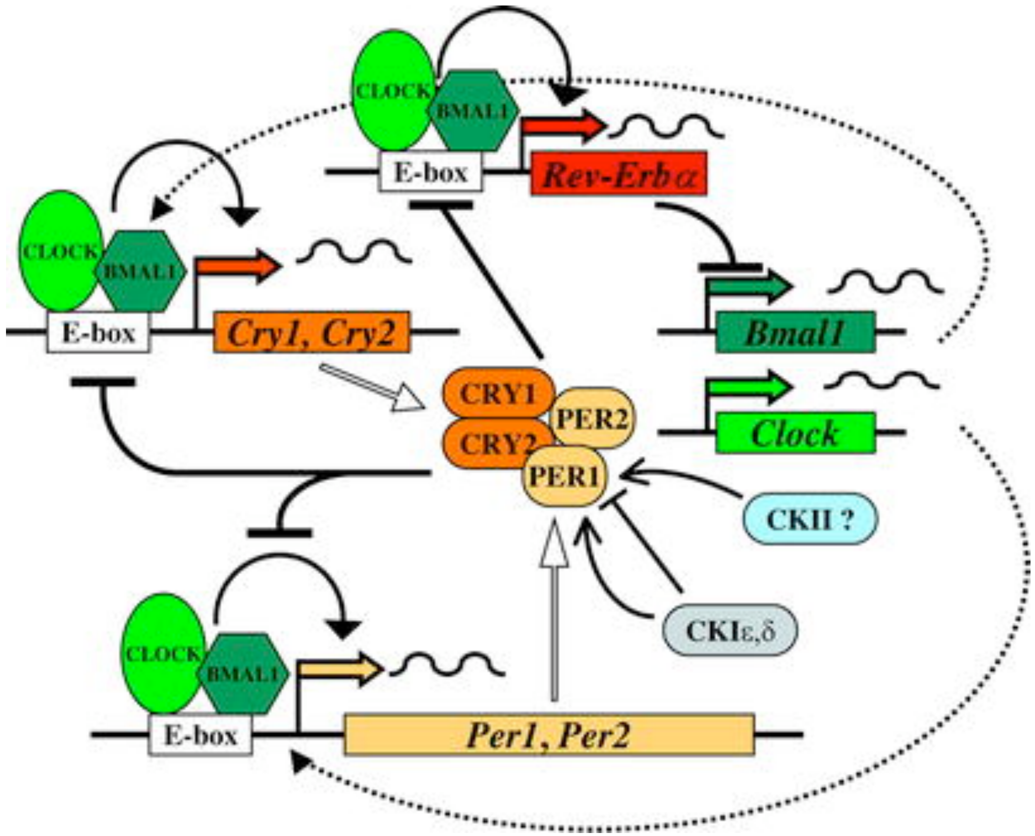


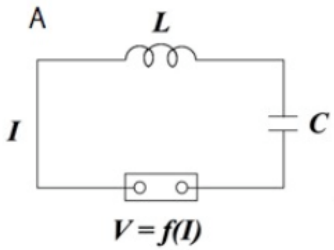
Figure from Gachon, Nagoshi, Brown, Ripperger, Schibler (2004) The mammalian circadian timing system: from gene expression to physiology. *Chromosomia* 113: 103-112.

First models for circadian clocks

Van der Pol Oscillator

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

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



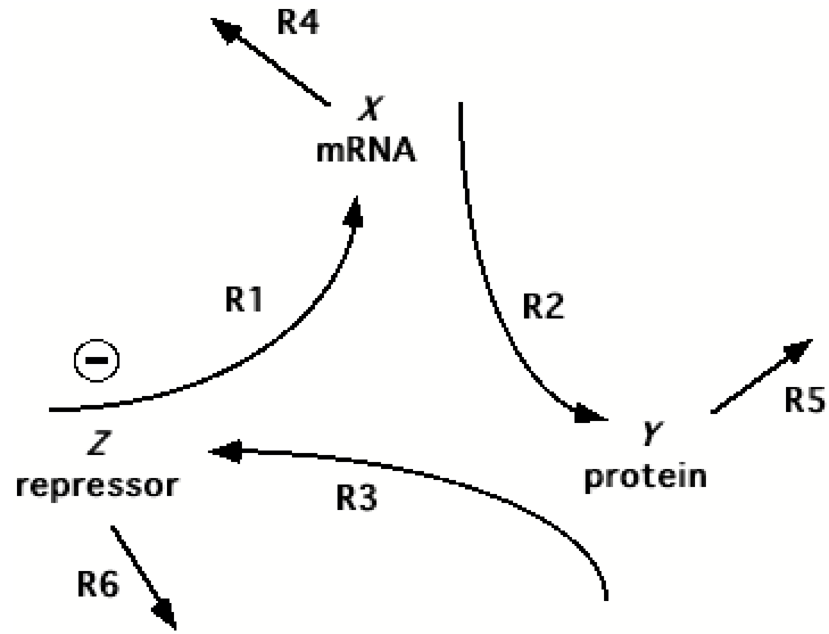
$$\frac{\mathrm{d}s(t)}{\mathrm{d}t} = z(t) + \epsilon\left(\frac{2\pi}{\tau}\right)\left[s(t) - \frac{4s(t)^3}{3\gamma^2}\right] + \left(\frac{2\pi}{\tau}\right)\gamma(1 - ms(t))CI(t)^{1/3} \qquad (3)$$

$$\frac{\mathrm{d}z(t)}{\mathrm{d}t} = -\left(\frac{2\pi}{\tau}\right)^2 s(t) + \frac{2\pi}{\tau} z(t)\left(\frac{1 - ms(t)}{3}\right)CI(t)^{1/3}$$

Kronauer RE, Czeisler CA, Pilato SF, Moore-Ede MC, Weitzman ED. (1982) Mathematical model of the human circadian system with two interacting oscillators. *Am J Physiol*. 242: R3-17.

First models for circadian clocks

Goodwin Model (1965)



$$\frac{dX}{dt} = \frac{k_1}{1+Z^n} - k_4 X$$

$$\frac{dY}{dt} = k_2 X - k_5 Y$$

$$\frac{dZ}{dt} = k_3 Y - k_6 Z$$

- negative feedback loop
- non-linearity
- delay

Goodwin BC (1965) Oscillatory behavior in enzymatic control processes. **In**: G. Weber, Editor, *Advances in Enzyme Regulation* **3**, Pergamon Press, Oxford, pp. 425-438.

Ruoff P, Vinsjevik M, Monnerjahn C, Rensing L. (1999) The Goodwin oscillator: on the importance of degradation reactions in the circadian clock. J Biol Rhythms. 14:469-79

Ruoff P, Rensing L (1996) The Temperature-Compensated Goodwin Oscillator Simulates Many Circadian Clock Properties. J. Theor. Biol. 179:275- 285.

Characterization of *per* gene in *Drosophila*

Feedback of the *Drosophila period* gene product on circadian cycling of its messenger RNA levels

Hardin PE, Hall JC, Rosbash M.

Nature (1990) 343: 536-40.

Circadian oscillations in *period* gene mRNA levels are transcriptionally regulated

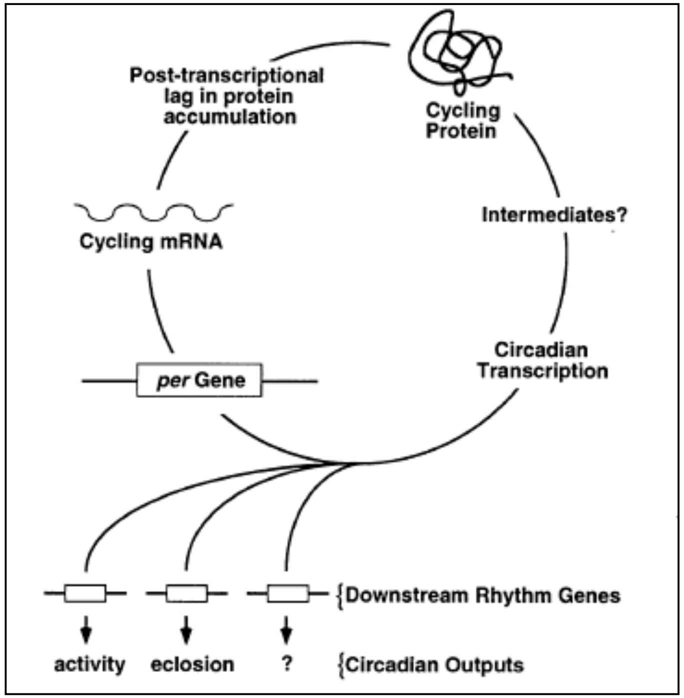
Hardin PE, Hall JC, Rosbash M.

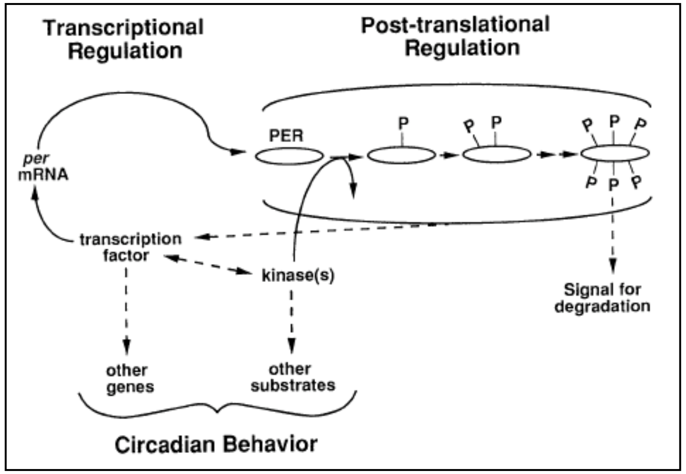
Proc Natl Acad Sci USA (1992) 89: 11711-5.

Temporal phosphorylation of the *Drosophila* period protein

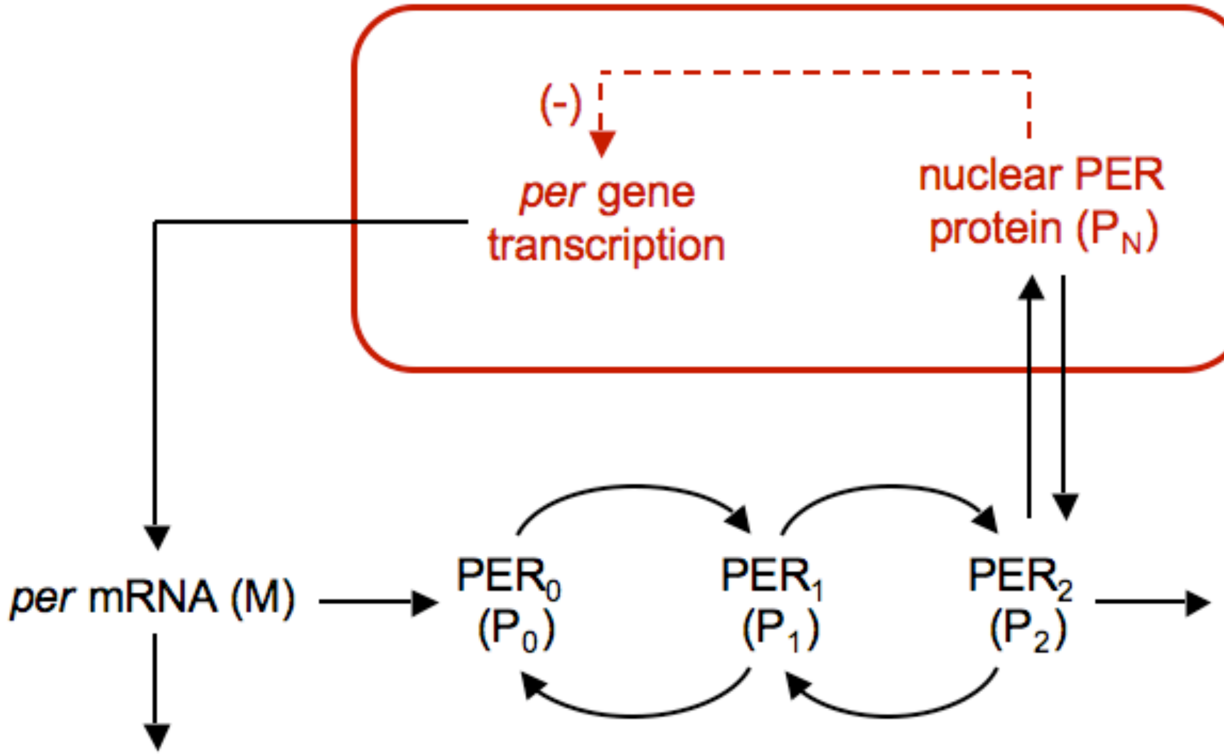
Edery I, Zwiebel LJ, Dembinska ME, Rosbash M.

Proc Natl Acad Sci USA (1994) 91: 2260-4.





Goldbeter's 5-variable model



Goldbeter A (1995) A model for circadian oscillations in the *Drosophila* period protein (PER). *Proc. R. Soc. Lond. B. Biol. Sci.* 261, 319-24.

Goldbeter's 5-variable model: equations

per mRNA

$$\frac{dM_P}{dt} = v_s \frac{K_I^n}{K_I^n + P_N^n} - v_m \frac{M_P}{K_m + M_P}$$

PER protein (unphosph.)

$$\frac{dP_0}{dt} = k_s M_P - v_1 \frac{P_0}{K_1 + P_0} + v_2 \frac{P_1}{K_2 + P_1}$$

PER protein (monophosph.)

$$\frac{dP_1}{dt} = v_1 \frac{P_0}{K_1 + P_0} - v_2 \frac{P_1}{K_2 + P_1} - v_3 \frac{P_1}{K_3 + P_1} + v_4 \frac{P_2}{K_4 + P_2}$$

PER protein (biphosph.)

$$\frac{dP_2}{dt} = v_3 \frac{P_1}{K_3 + P_1} - v_4 \frac{P_2}{K_4 + P_2} - v_d \frac{P_2}{K_d + P_2} - k_1 P_2 + k_2 P_N$$

nuclear PER protein

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

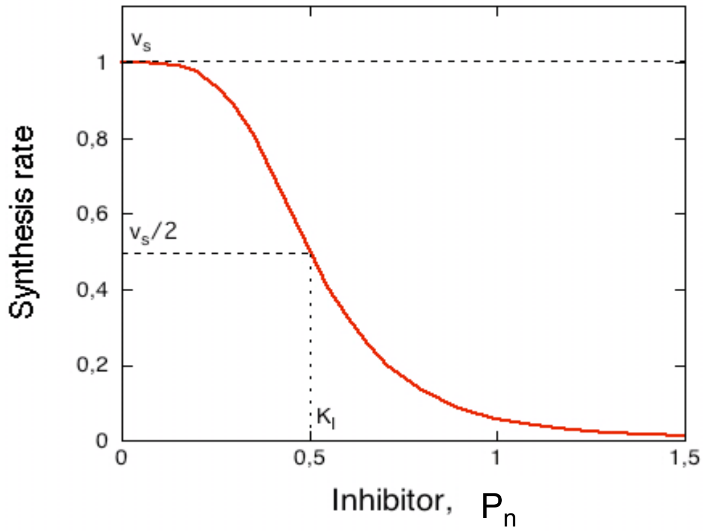
Goldbeter A (1995) A model for circadian oscillations in the *Drosophila* period protein (PER). *Proc. R. Soc. Lond. B. Biol. Sci.* 261, 319-24.

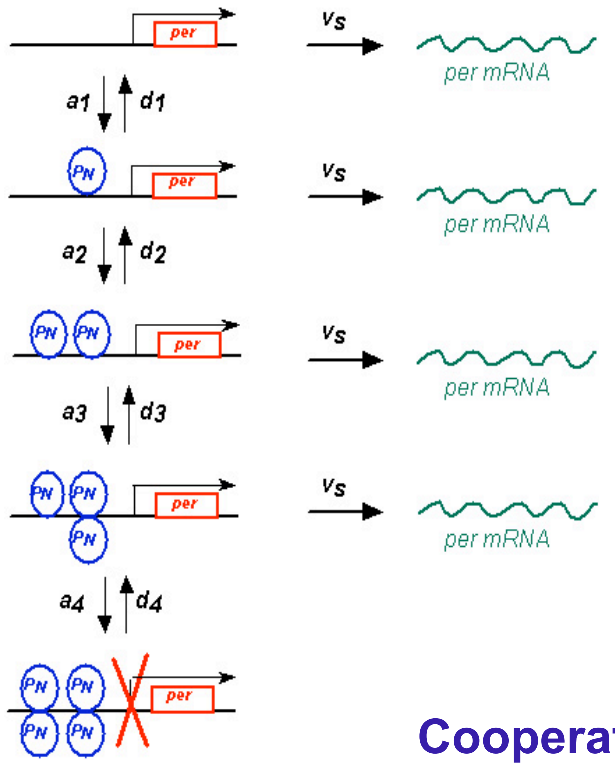
Goldbeter's 5-variable model: equations

Dynamics of *per* mRNA (M_P): synthesis

$$\frac{dM_P}{dt} = \boxed{v_s \frac{K_I^n}{K_I^n + P_N^n}} - v_m \frac{M_P}{K_m + M_P}$$

Inhibition: Hill function





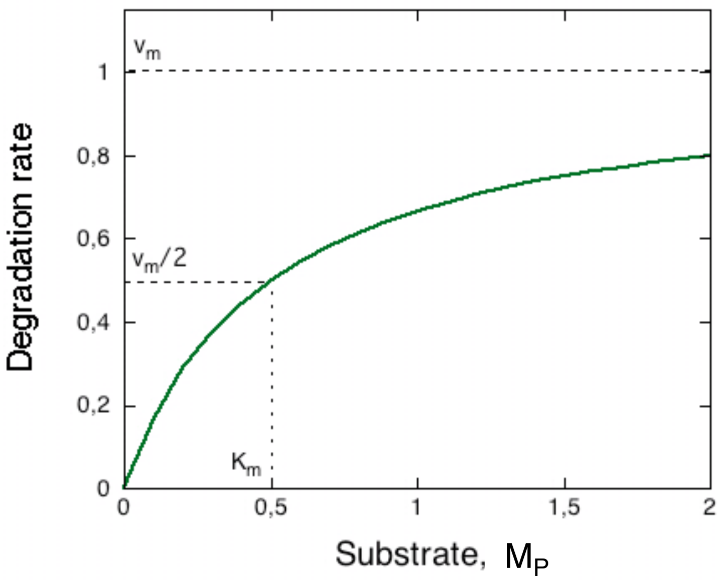
Cooperativity

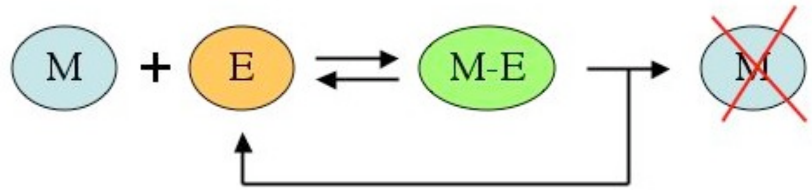
Goldbeter's 5-variable model: equations

Dynamics of *per* mRNA (M_P): degradation

$$\frac{dM_P}{dt} = v_s \frac{K_I^n}{K_I^n + P_N^n} - \boxed{v_m \frac{M_P}{K_m + M_P}}$$

Degradation: Michaelis-Menten





$E << M$

$k_1, k_{-1} >> k_2$

$E_{tot} = E + ME$

$$\boxed{K_M = (k_{-1} + k_2) / k_1 \qquad v_m = k_2 E_{tot}}$$

Goldbeter's 5-variable model: equations

Dynamics of PER protein (P_0, P_1, P_2, P_N)

$$\frac{dP_0}{dt} = \boxed{k_s M_P} - v_1 \frac{P_0}{K_1 + P_0} + v_2 \frac{P_1}{K_2 + P_1}$$

PER synthesis:
proportional to mRNA

$$\frac{dP_1}{dt} = v_1 \frac{P_0}{K_1 + P_0} - v_2 \frac{P_1}{K_2 + P_1} - v_3 \frac{P_1}{K_3 + P_1} + v_4 \frac{P_2}{K_4 + P_2}$$

$$\frac{dP_2}{dt} = v_3 \frac{P_1}{K_3 + P_1} - v_4 \frac{P_2}{K_4 + P_2} - v_d \frac{P_2}{K_d + P_2} - k_1 P_2 + k_2 P_N$$

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

Goldbeter's 5-variable model: equations

Dynamics of PER protein (*P_0 , P_1 , P_2 , P_N*)

$$\frac{dP_0}{dt} = k_s M_P - \boxed{v_1 \frac{P_0}{K_1 + P_0} + v_2 \frac{P_1}{K_2 + P_1}}$$

PER phosphorylation/dephosphorylation:
Michaelis-Menten

$$\frac{dP_1}{dt} = \boxed{v_1 \frac{P_0}{K_1 + P_0} - v_2 \frac{P_1}{K_2 + P_1}} - \boxed{v_3 \frac{P_1}{K_3 + P_1} + v_4 \frac{P_2}{K_4 + P_2}}$$

PER phosphorylation/dephosphorylation:
Michaelis-Menten

$$\frac{dP_2}{dt} = \boxed{v_3 \frac{P_1}{K_3 + P_1} - v_4 \frac{P_2}{K_4 + P_2}} - v_d \frac{P_2}{K_d + P_2} - k_1 P_2 + k_2 P_N$$

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

Goldbeter's 5-variable model: equations

Dynamics of PER protein (*P_0, P_1, P_2, P_N*)

$$\frac{dP_0}{dt} = k_s M_P - v_1 \frac{P_0}{K_1 + P_0} + v_2 \frac{P_1}{K_2 + P_1}$$

$$\frac{dP_1}{dt} = v_1 \frac{P_0}{K_1 + P_0} - v_2 \frac{P_1}{K_2 + P_1} - v_3 \frac{P_1}{K_3 + P_1} + v_4 \frac{P_2}{K_4 + P_2}$$

$$\frac{dP_2}{dt} = v_3 \frac{P_1}{K_3 + P_1} - v_4 \frac{P_2}{K_4 + P_2} - \boxed{v_d \frac{P_2}{K_d + P_2}} - k_1 P_2 + k_2 P_N$$

PER degradation: Michaelis-Menten

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

Goldbeter's 5-variable model: equations

Dynamics of PER protein (P_0 , P_1 , P_2 , P_N)

$$\frac{dP_0}{dt} = k_s M_P - v_1 \frac{P_0}{K_1 + P_0} + v_2 \frac{P_1}{K_2 + P_1}$$

$$\frac{dP_1}{dt} = v_1 \frac{P_0}{K_1 + P_0} - v_2 \frac{P_1}{K_2 + P_1} - v_3 \frac{P_1}{K_3 + P_1} + v_4 \frac{P_2}{K_4 + P_2}$$

$$\frac{dP_2}{dt} = v_3 \frac{P_1}{K_3 + P_1} - v_4 \frac{P_2}{K_4 + P_2} - v_d \frac{P_2}{K_d + P_2} - \boxed{k_1 P_2 + k_2 P_N}$$

PER nuclear transport: linear

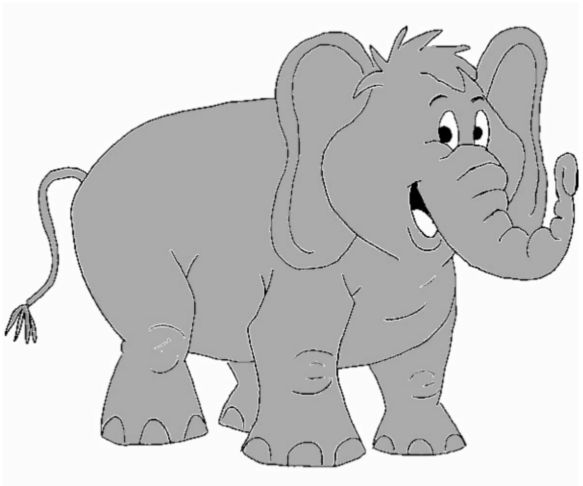
$$\frac{dP_N}{dt} = \boxed{k_1 P_2 - k_2 P_N}$$

Goldbeter's 5-variable model: parameters

Parameter values

The values of the kinetic parameters are (usually) not known.

They are taken in the physiological range in order to satisfy the constraints (self-sustained oscillations, period of 24h, phase relationship, entrainment by light-dark cycles,...).



With four parameters, I can fit an elephant, and with five I can make him wiggle trunk.

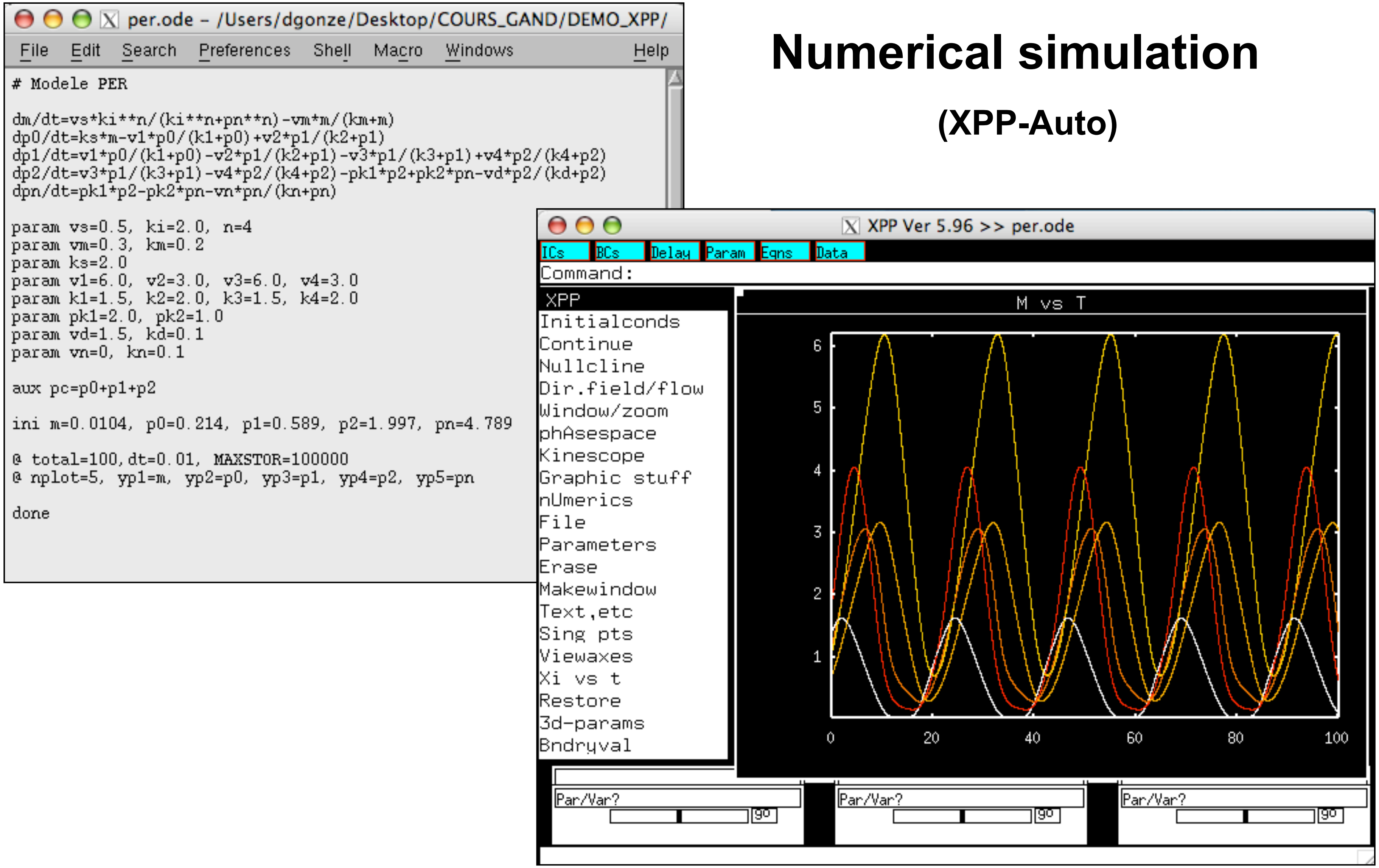
(attributed to J. von Neumann by E. Fermi)

Source: Dyson (2004) *Nature* 427:297.

Goldbeter's 5-variable model: simulation

Numerical simulation

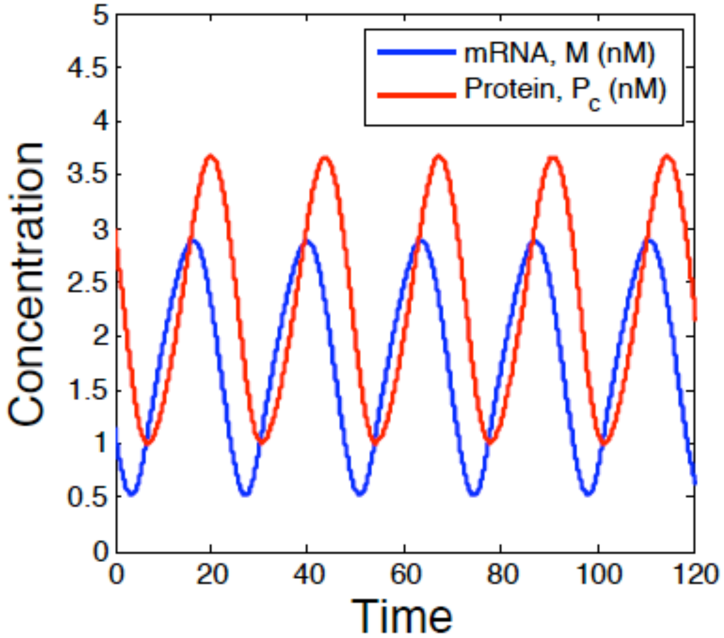
(XPP-Auto)

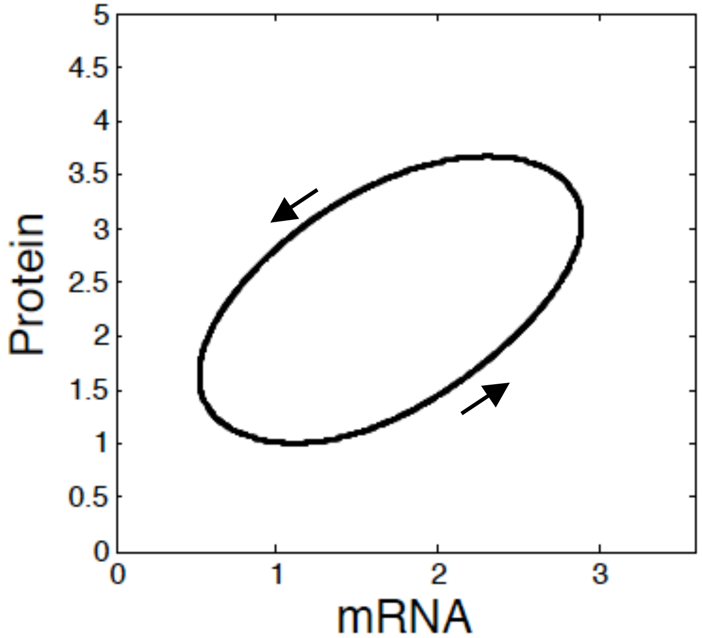


XPP-AUTO: http://www.math.pitt.edu/~bard/xpp/xpp.html

Goldbeter's 5-variable model: results

Self-sustained (limit cycle) oscillations



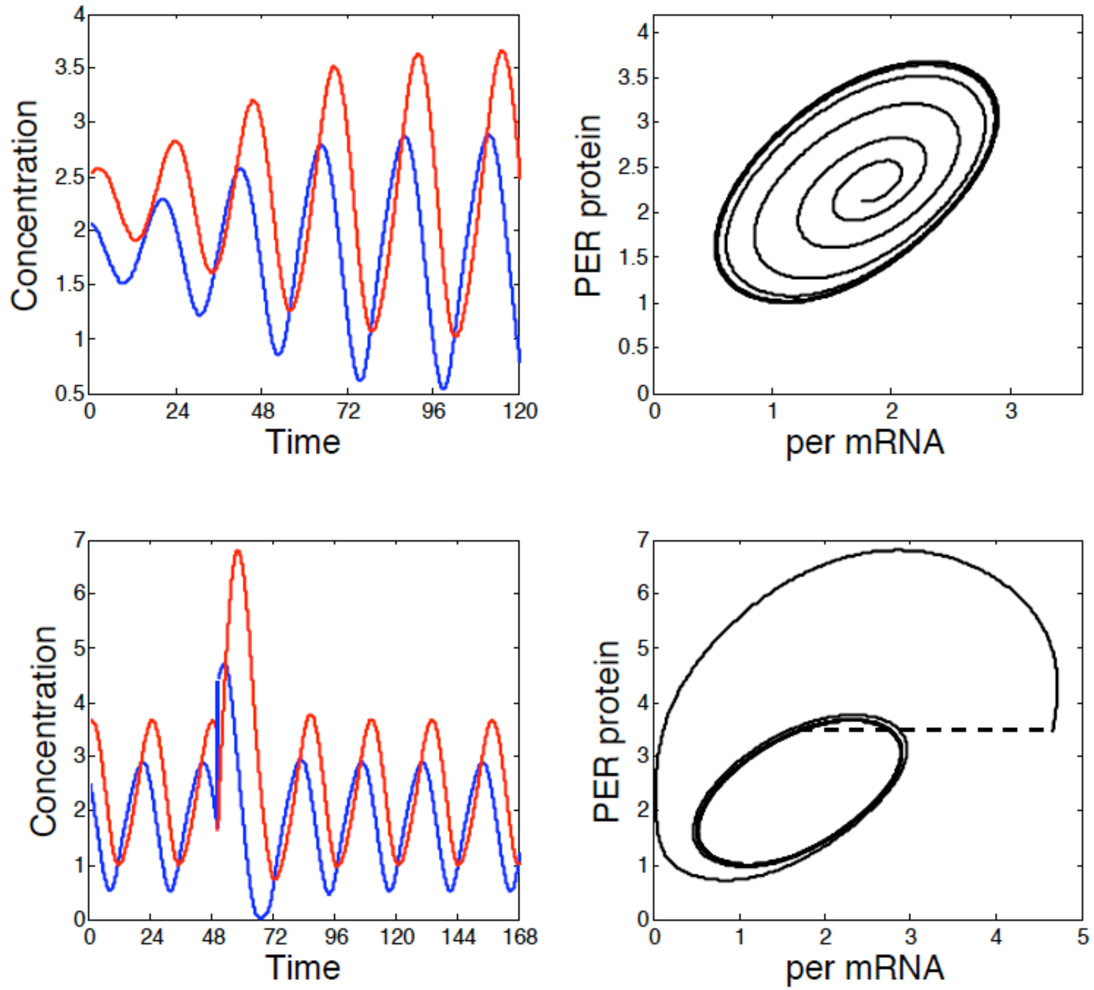


Limit-cycle oscillations are characterized by a fixed amplitude and a fixed period. Such oscillations correspond to a close curve in the phase space, i.e. the space of the variables. They are robust in the sense that if a perturbation is exerted on such a system, the system will automatically come back to its "normal" behavior, i.e. to the limit cycle.

Goldbeter A (1995) *Proc. R. Soc. Lond. B. Biol. Sci.* 261, 319-24.

Goldbeter's 5-variable model: results

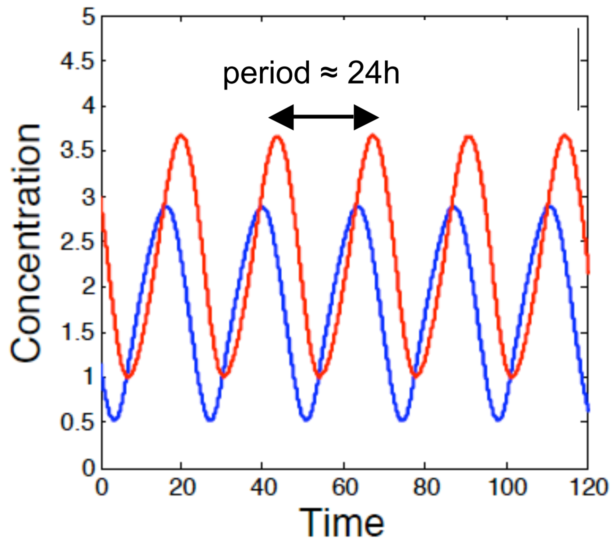
Self-sustained (limit cycle) oscillations

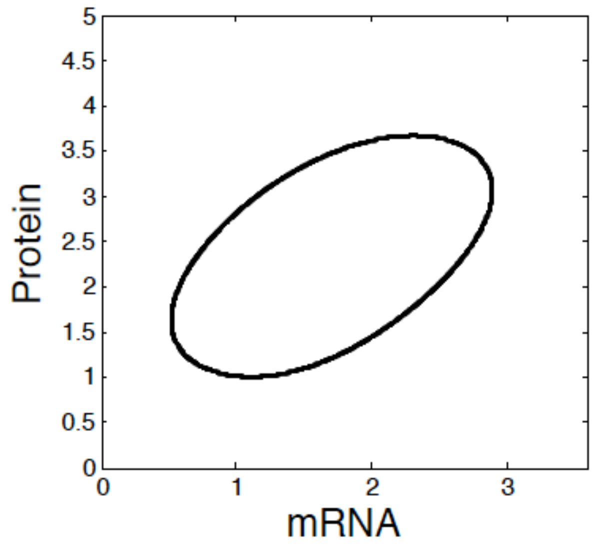


Goldbeter A (1995) *Proc. R. Soc. Lond. B. Biol. Sci.* 261, 319-24.

Goldbeter's 5-variable model: results

Self-sustained (limit cycle) oscillations

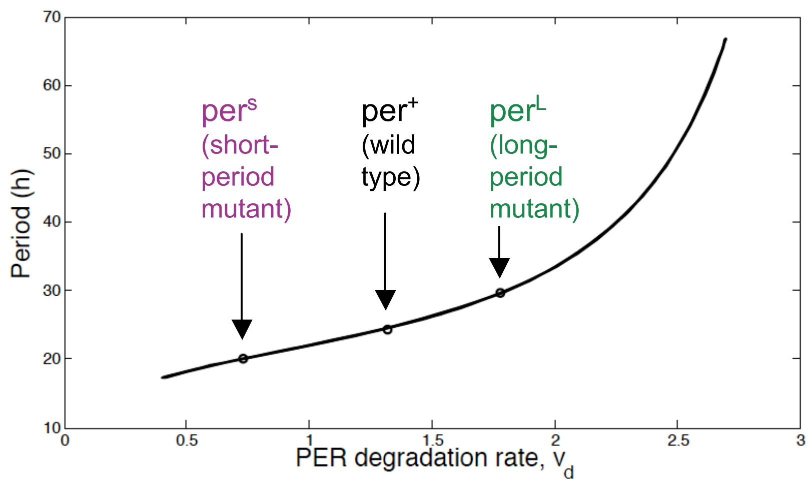




Mutants:

per^l long-period mutant
per^s short-period mutant

The *per* mutants can be explained by a change in the protein degradation rate.



Effect of light on the circadian clock

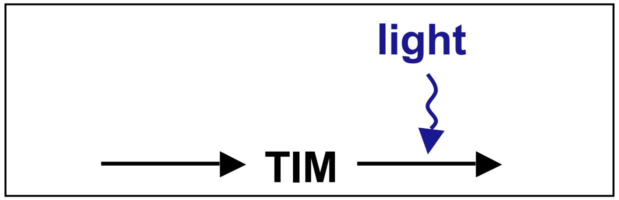
Effect of light on the circadian clock

Light-induced degradation of TIMELESS and entrainment of the Drosophila circadian clock.
Myers MP, Wager-Smith K, Rothenfluh-Hilfiker A, Young MW
Science (1996) 271: 1736-1740.

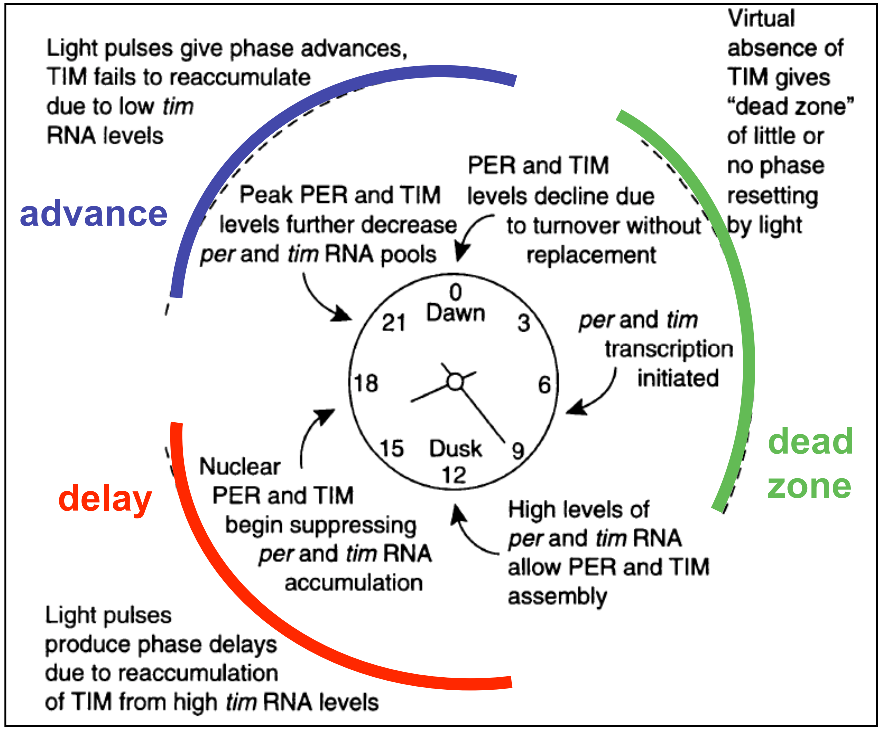
Resetting the *Drosophila* clock by photic regulation of PER and a PER-TIM complex.
Lee C, Parikh V, Itsukaichi T, Bae K, Edery I
Science (1996) 271:1740-4.

A light-entrainment mechanism for the *Drosophila* circadian clock.
Zeng H, Qian Z, Myers MP, Rosbash M
Nature (1996) 380: 129-135.

Regulation of the *Drosophila* protein timeless suggests a mechanism for resetting the circadian clock by light.
Hunter-Ensor M, Ousley A, Sehgal A
Cell (1996) 84: 677-85.

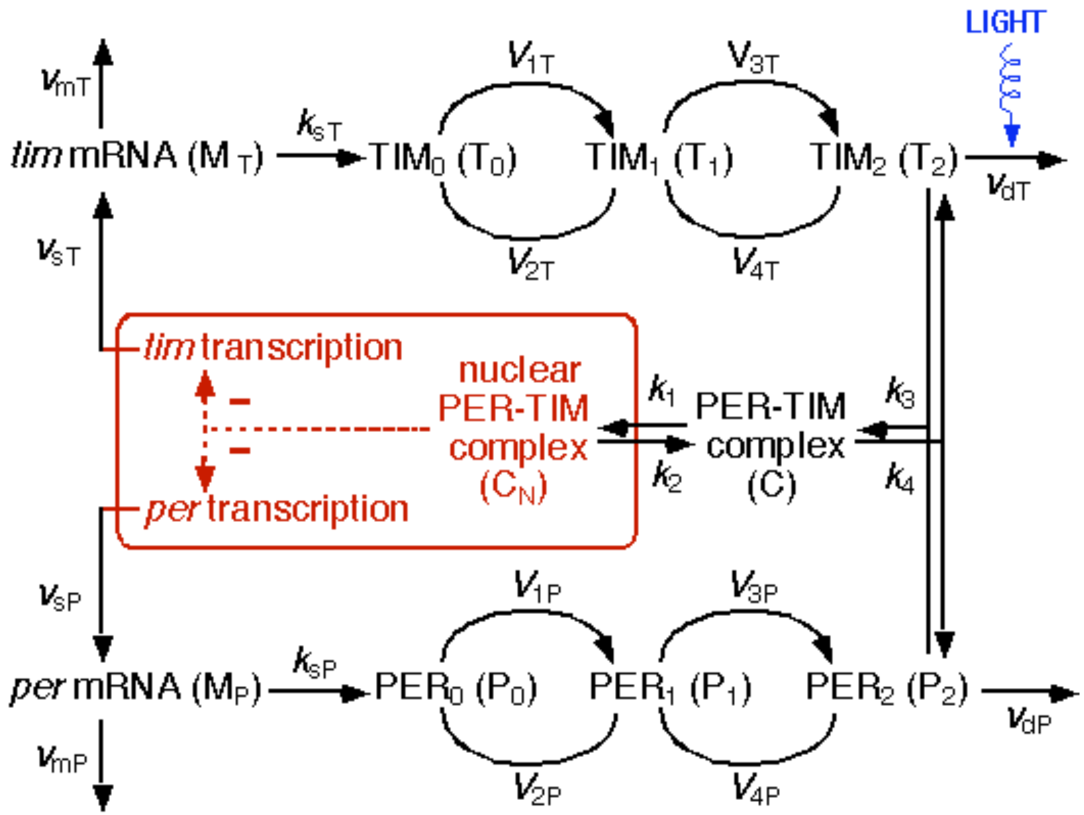


- Light activates TIM degradation
- TIM and PER form a complex
- Transcription of *tim* is co-regulated with *per*



Leloup-Goldbeter's 10-variable model

Extended model for the *Drosophila* circadian clock



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

Leloup-Goldbeter's 10-variable model

Extended model for the *Drosophila* circadian clock

***per* mRNA**

$$\frac{dM_P}{dt} = v_{sP}\frac{K_{IP}^{\,n}}{K_{IP}^{\,n} + C_N^{\,n}} - v_{mP}\frac{M_P}{K_{mP} + M_P} - k_d M_P$$

PER protein

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

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

$$\frac{dP_2}{dt} = V_{3P}\frac{P_1}{K_{3P} + P_1} - V_{4P}\frac{P_2}{K_{4P} + P_2} - k_3 P_2 T_2 + k_4 C - v_{dP}\frac{P_2}{K_{dP} + P_2} - k_d P_2$$

***tim* mRNA**

$$\frac{dM_T}{dt} = v_{sT}\frac{K_{IT}^{\,n}}{K_{IT}^{\,n} + C_N^{\,n}} - v_{mT}\frac{M_T}{K_{mT} + M_T} - k_d M_T$$

TIM protein

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

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

$$\frac{dT_2}{dt} = V_{3T}\frac{T_1}{K_{3T} + T_1} - V_{4T}\frac{T_2}{K_{4T} + T_2} - k_3 P_2 T_2 + k_4 C - v_{dT}\frac{T_2}{K_{dT} + T_2} - k_d T_2$$

PER-TIM complex

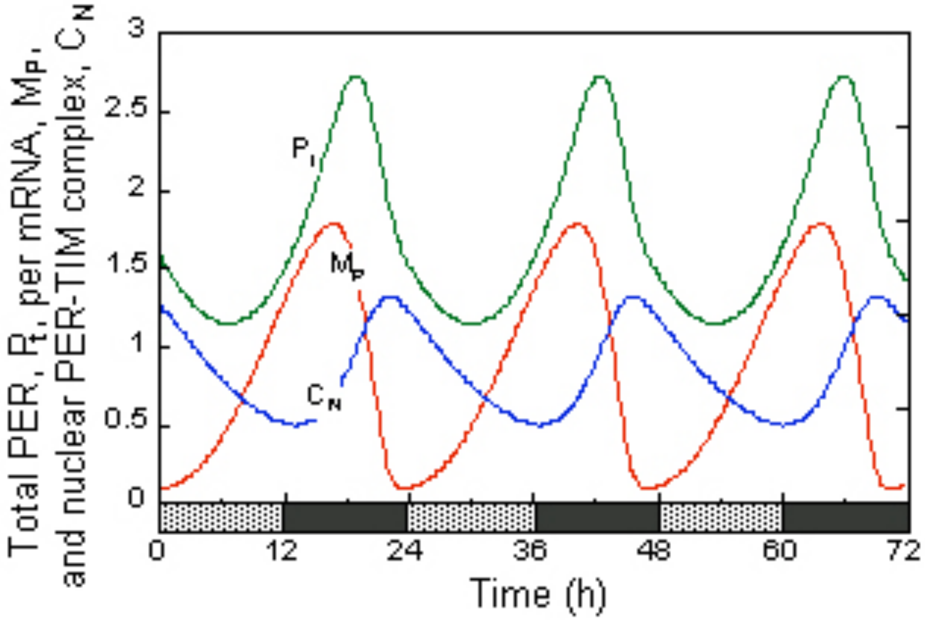
$$\frac{dC}{dt} = k_3 P_2 T_2 - k_4 C - k_1 C + k_2 C_N - k_{dC} C$$

$$\frac{dC_N}{dt} = k_1 C - k_2 C_N - k_{dN} C_N$$

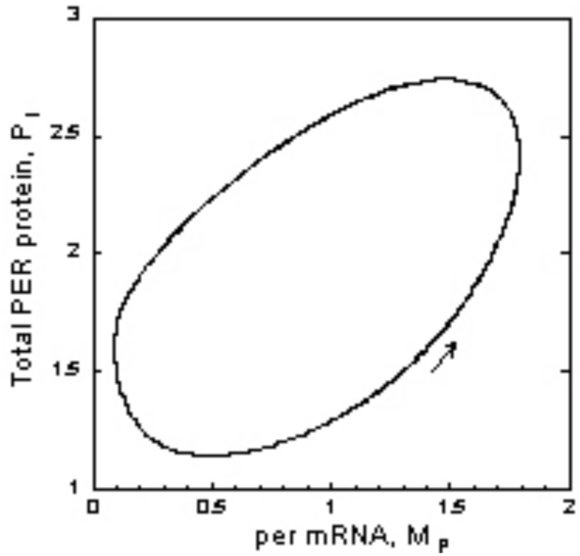
Leloup J-C & Goldbeter A (1998) A model for circadian rhythm in *Drosophila* incorporating the formation of a complex between the PER and TIM protein. *J. Biol. Rhythms.* 13: 70-87.

Leloup-Goldbeter's 10-variable model

Self-sustained oscillations



Limit cycle

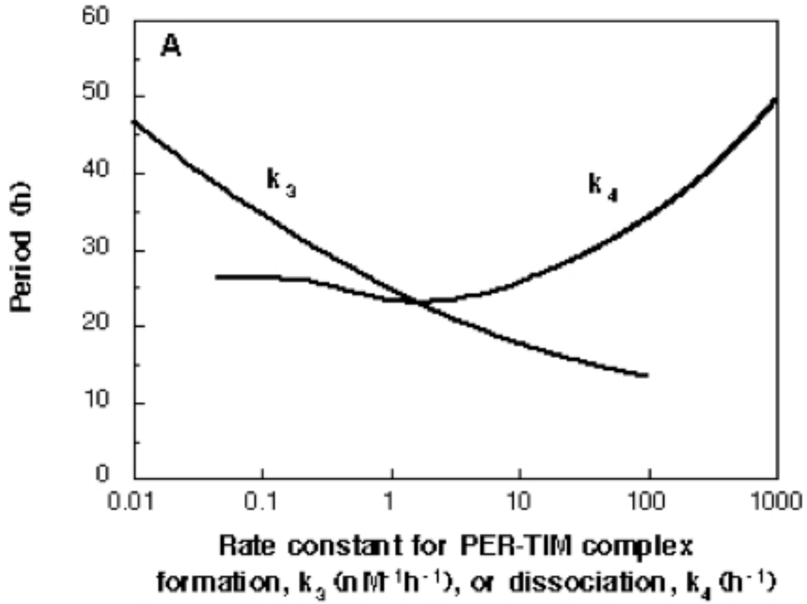


Leloup-Goldbeter's 10-variable model

Influence of parameters on the period of oscillations:

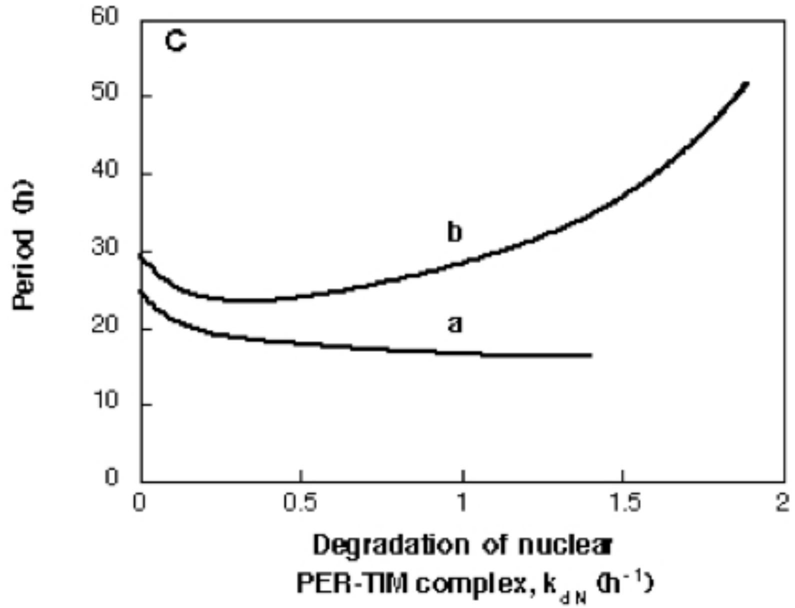
Bifurcation diagrams

Long period (*per*^{L}) mutant



k_3 PER-TIM complex formation
k_4 PER-TIM complex dissociation

Short period (*per*^{S}) mutant



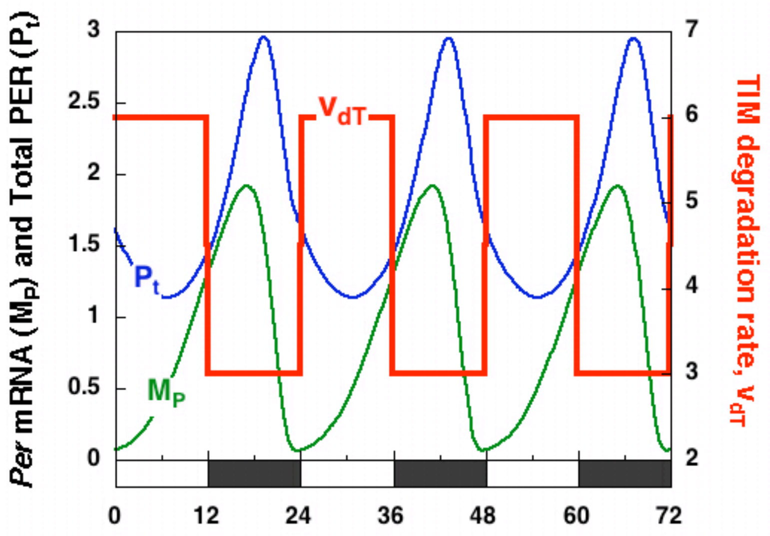
k_{dN} PER-TIM complex degradation
(a),(b) : two different parameter sets

Leloup-Goldbeter's 10-variable model

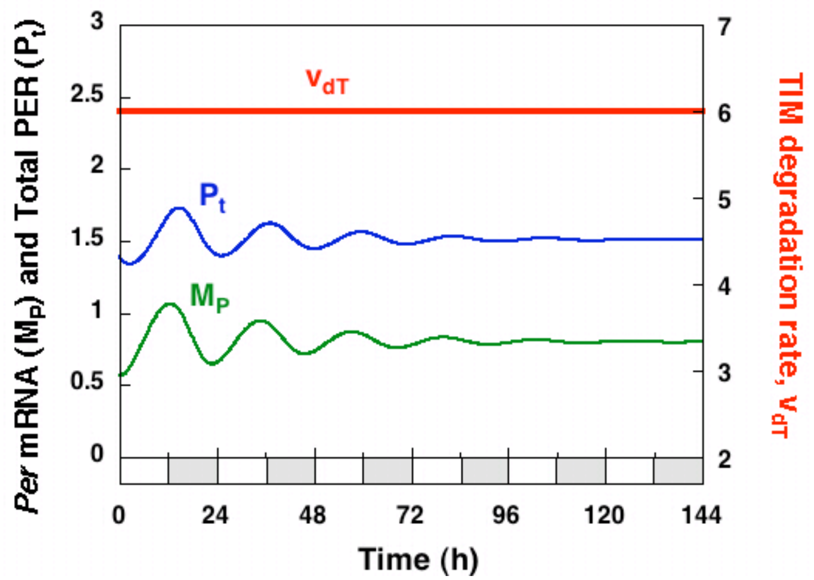
Modeling the effect of light

The effect of light can be modeled by modulation of parameter v_{dT} (TIM degradation rate). Light-dark cycles can thus be simulated by a periodic variation of v_{dT} (sine or square wave).

Entrainment by light-dark cycles

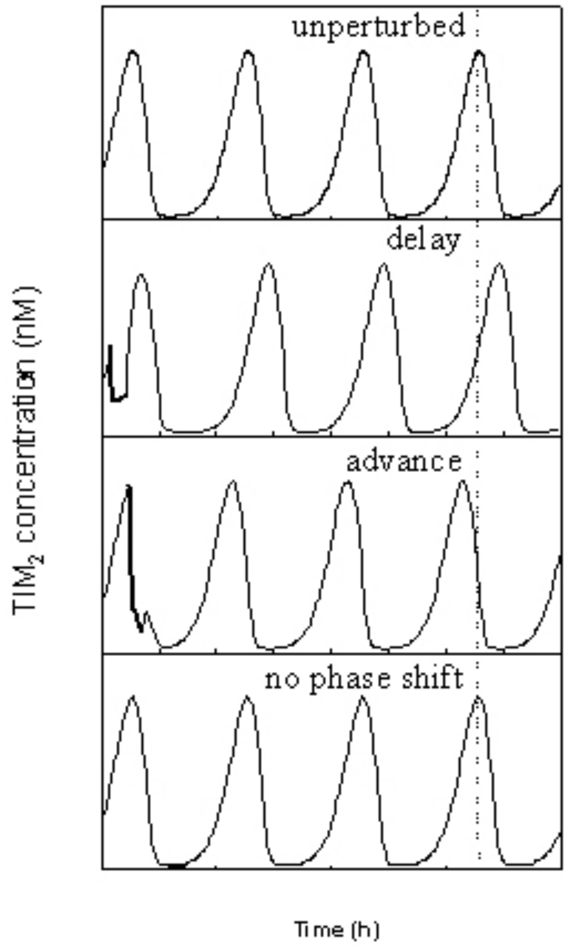


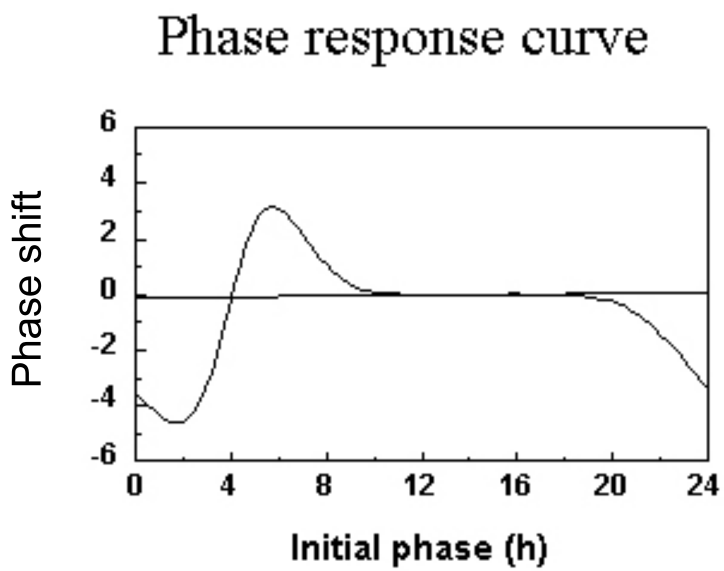
Damped oscillations in constant light



Leloup-Goldbeter's 10-variable model

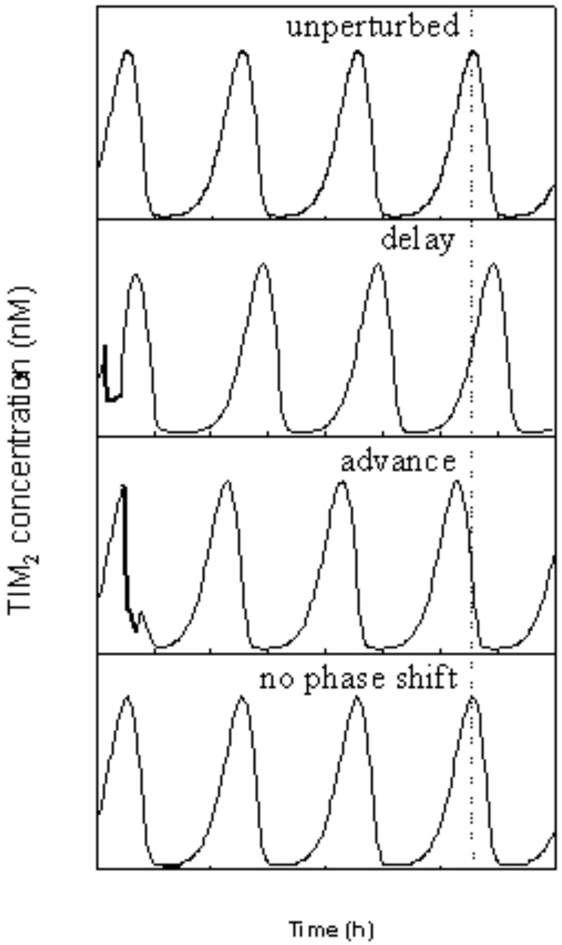
Phase shifting by a light pulse

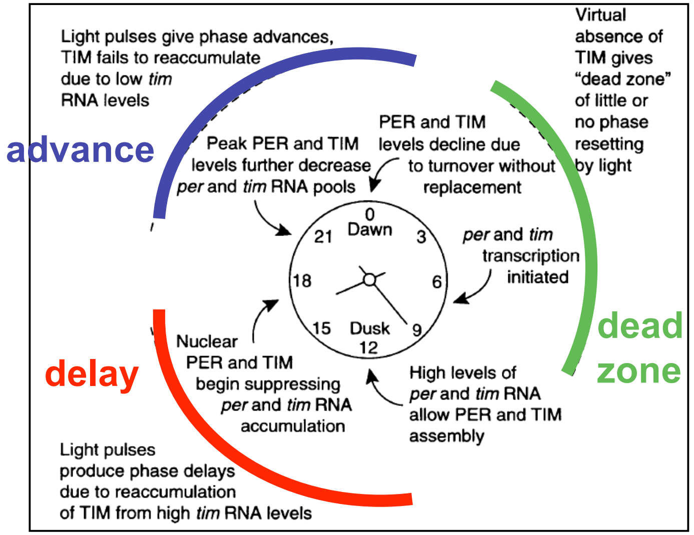




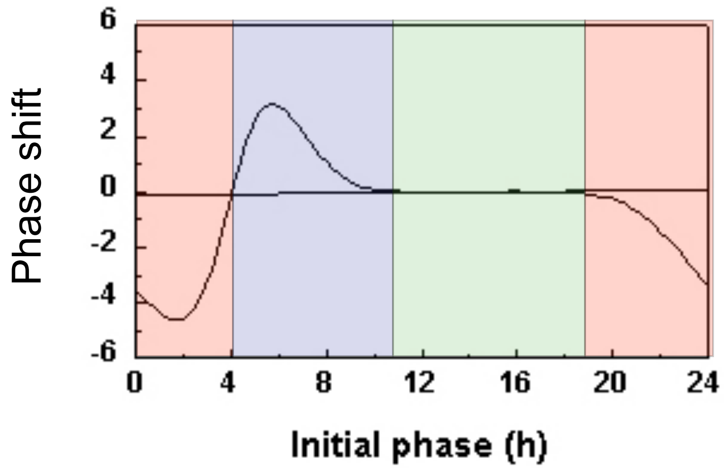
Leloup-Goldbeter's 10-variable model

Phase shifting by a light pulse





Phase response curve

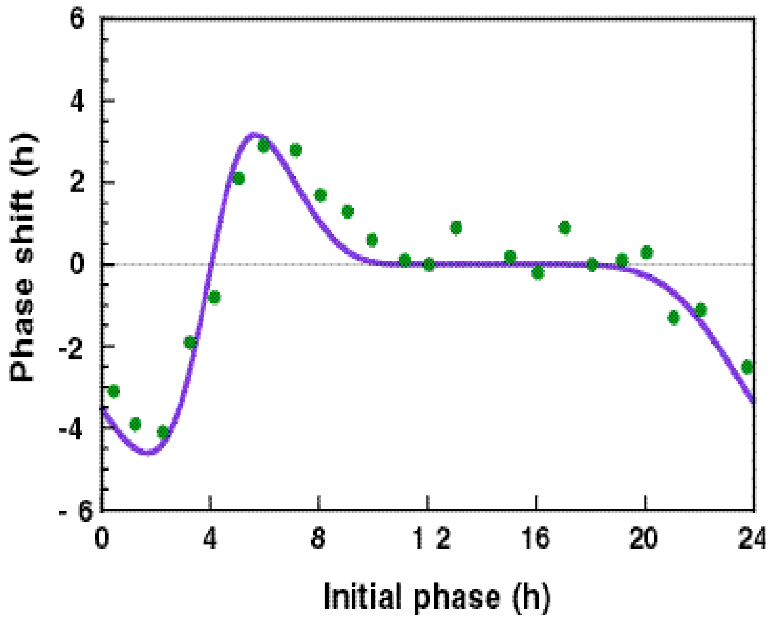


Leloup-Goldbeter's 10-variable model

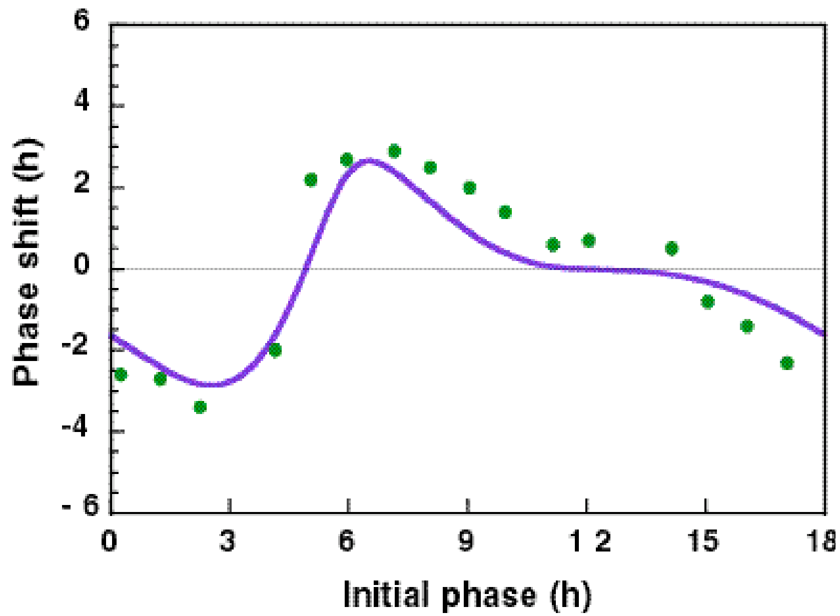
Phase shifting and PRC

comparison with experimental data

Wild type



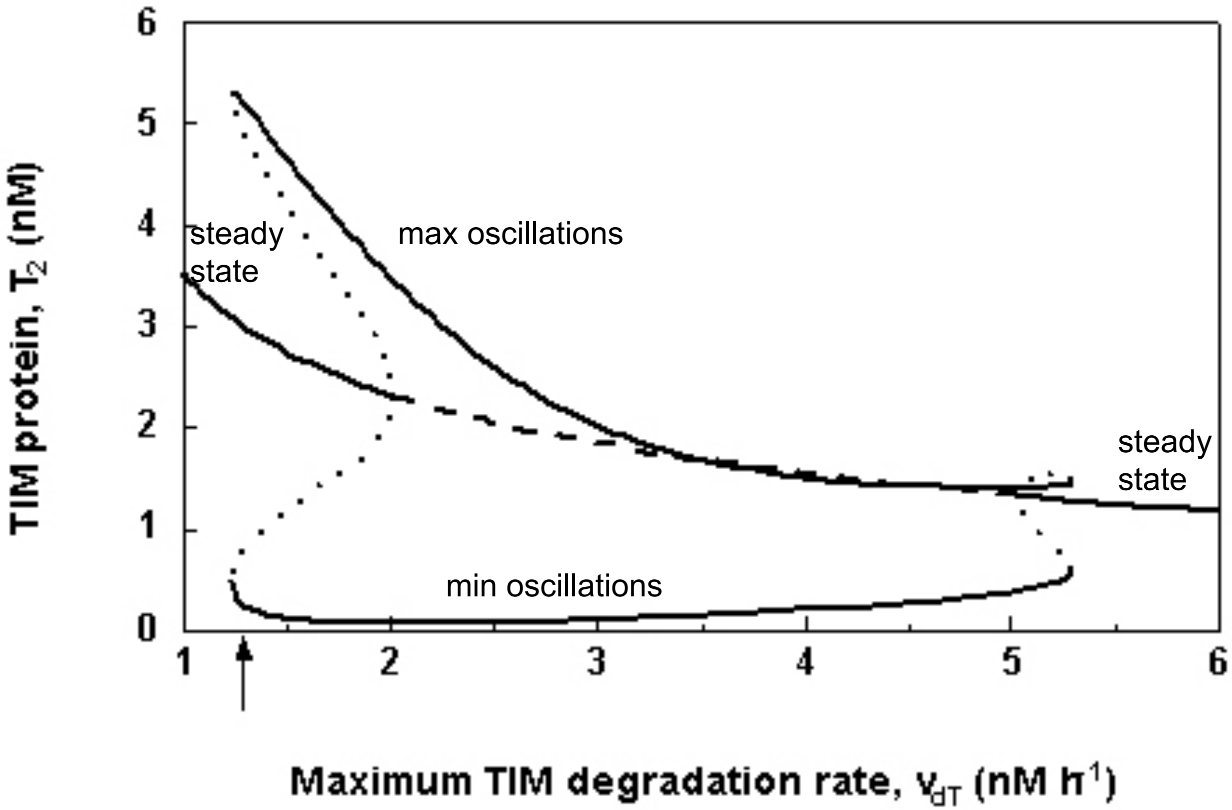
Short period mutant



- Experimental data (Hall JC & Rosbash M (1987) Genes and biological rhythms. *Trends Genet.* **3,** 185-91)
- Theoretical phase response curve (Leloup J-C & Goldbeter A (1998) *J. Biol. Rhythms.* **13**: 70-87)

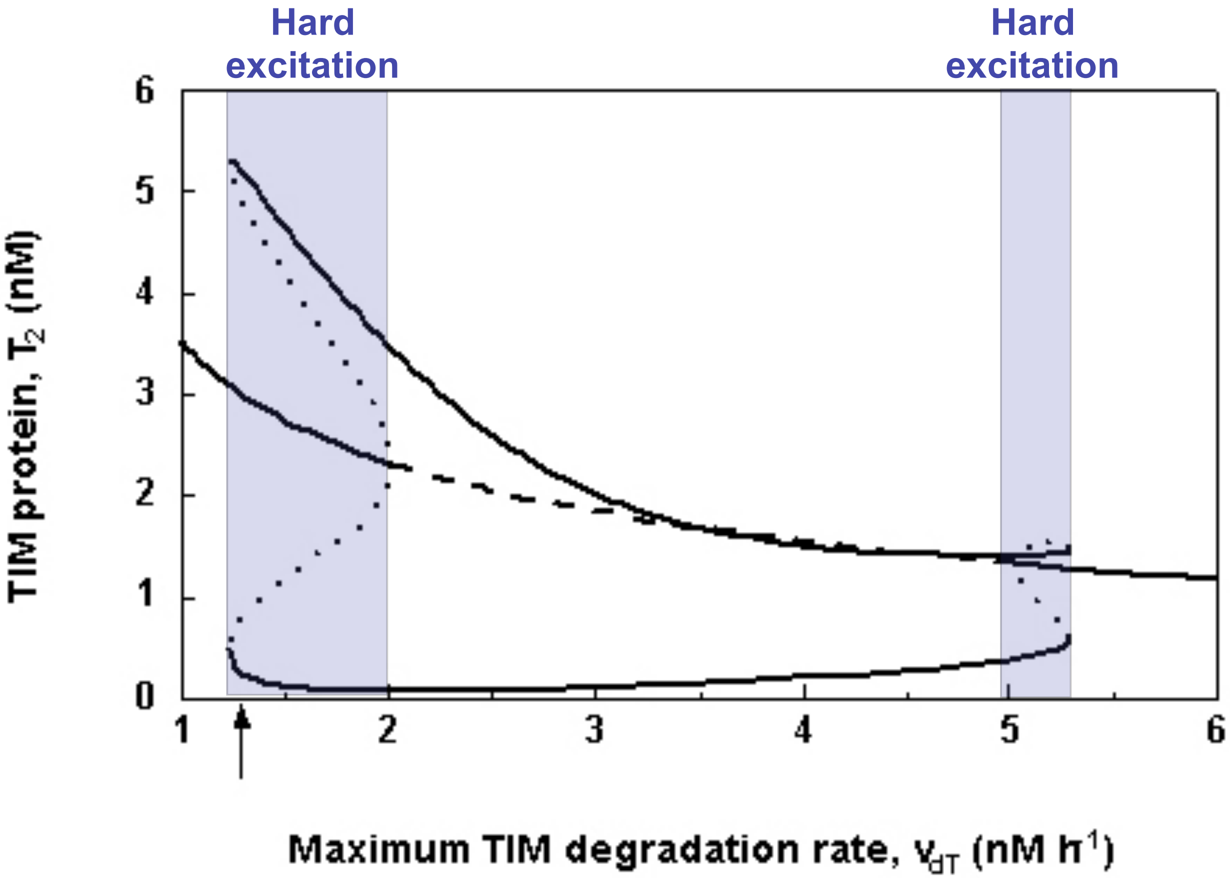
Leloup-Goldbeter's 10-variable model

Bifurcation diagram as a function of TIM degradation rate (v_{dT})



Leloup-Goldbeter's 10-variable model

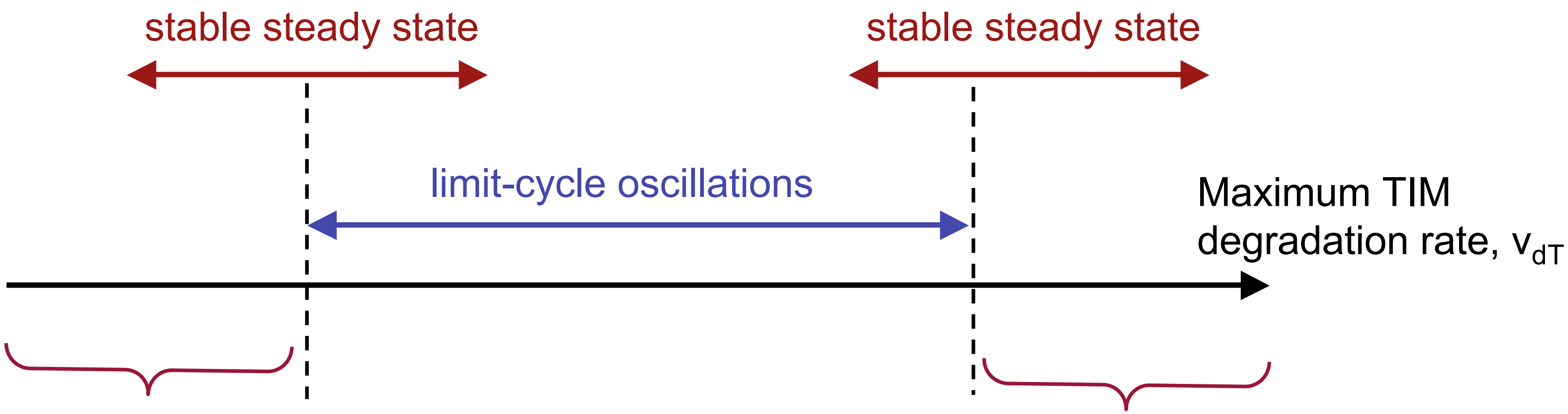
Bifurcation diagram as a function of TIM degradation rate (v_{dT})



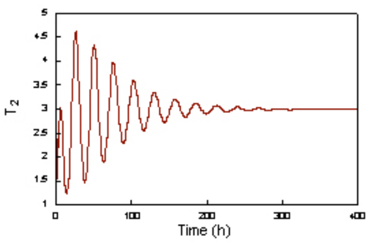
Hard excitation = coexistence between a stable steady state and stable oscillations

Leloup-Goldbeter's 10-variable model

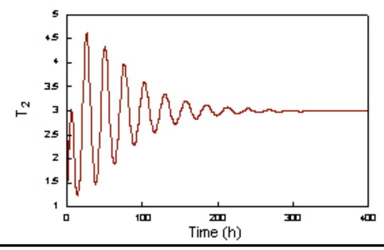
Interpretation of the bifurcation diagram



when v_{dT} is too small, only damped oscillations can be observed. The system ultimately converges to a steady state.

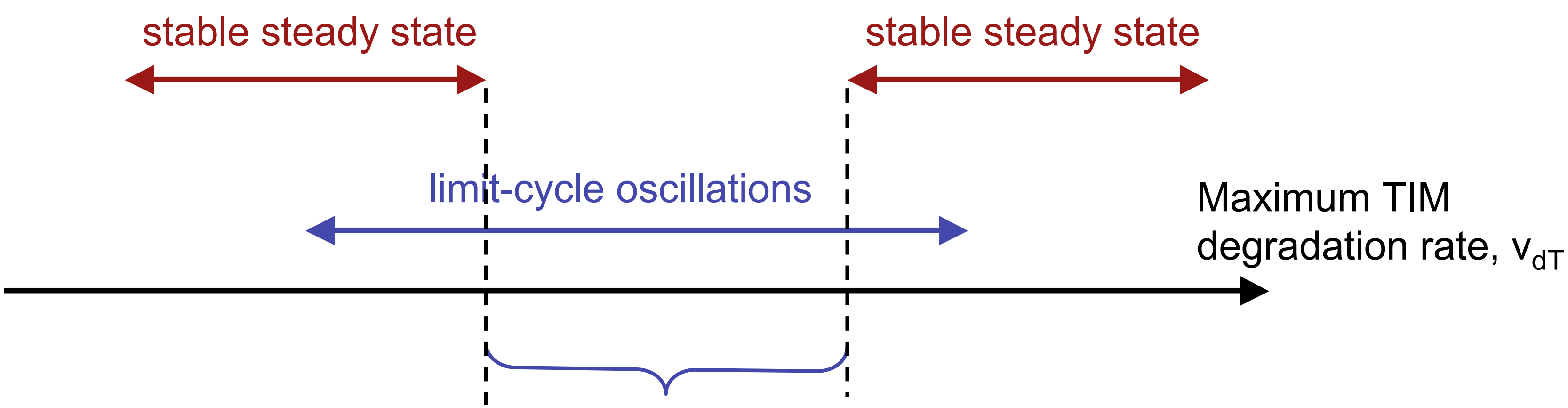


when v_{dT} is too large, only damped oscillations can be observed. The system ultimately converges to a steady state.

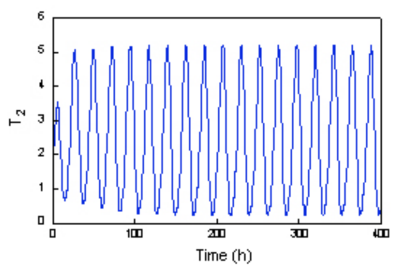


Leloup-Goldbeter's 10-variable model

Interpretation of the bifurcation diagram

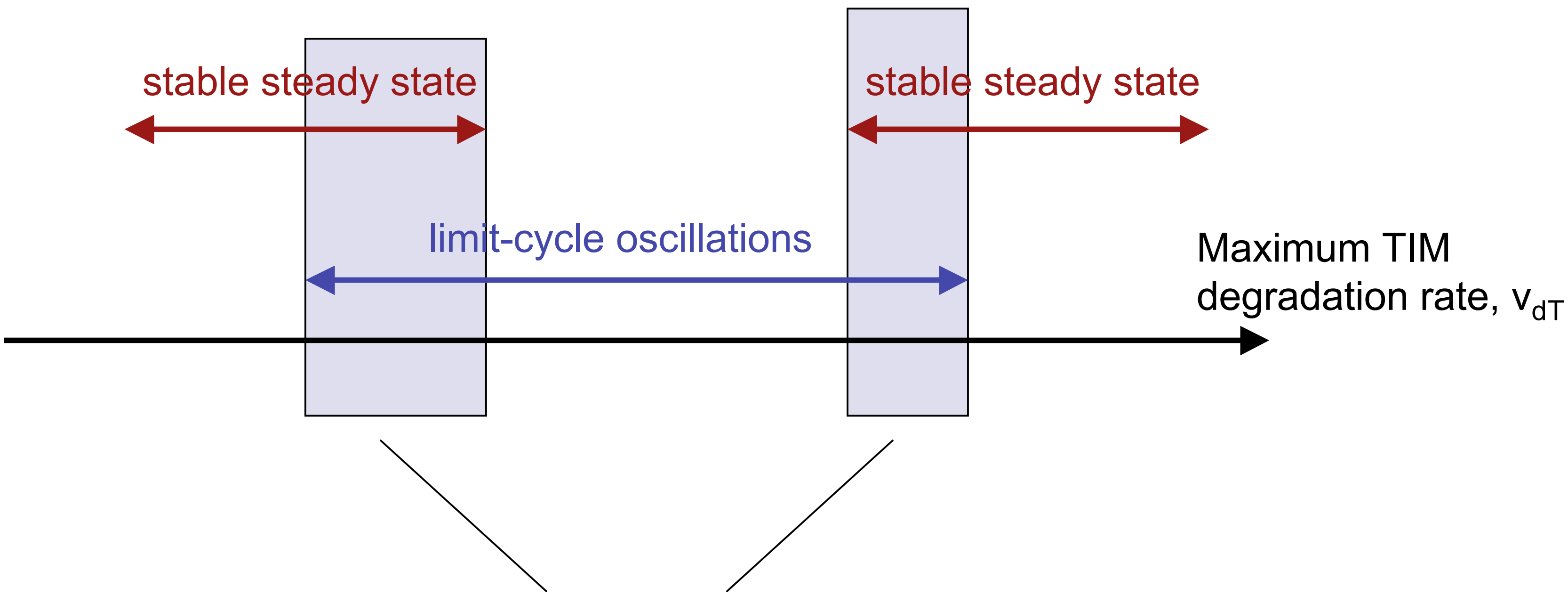


when v_{dT} is intermediary,
only limit-cycle oscillations
can be observed.



Leloup-Goldbeter's 10-variable model

Interpretation of the bifurcation diagram

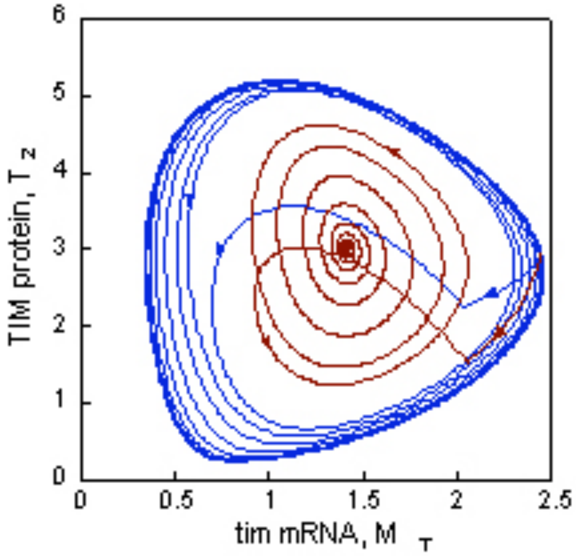


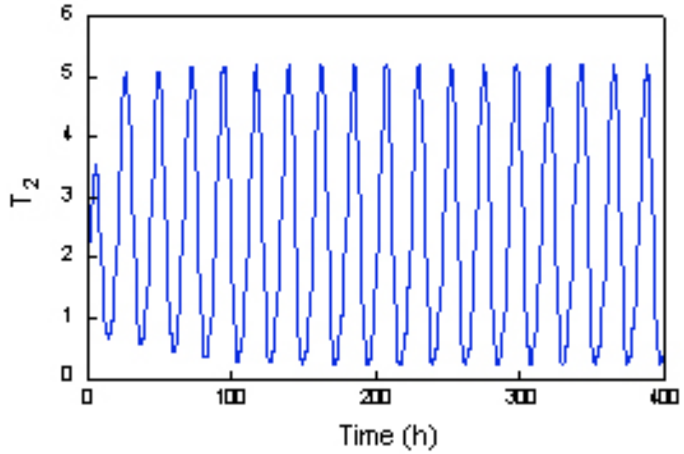
In these intermediary regions, the system has the choice: it can either oscillate or converge to a steady state. This choice depends on the initial state of the system. This property is called *hard excitation*.

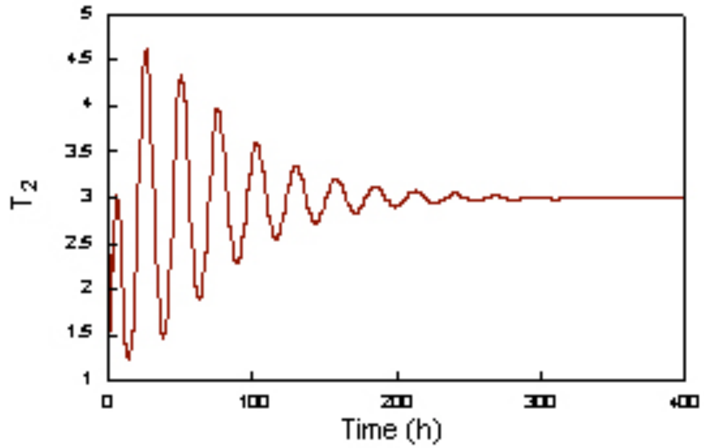
Leloup-Goldbeter's 10-variable model

Suppression of oscillations by a light pulse

Depending on the initial conditions, the system can either display self-sustained oscillations of converge to a steady state.



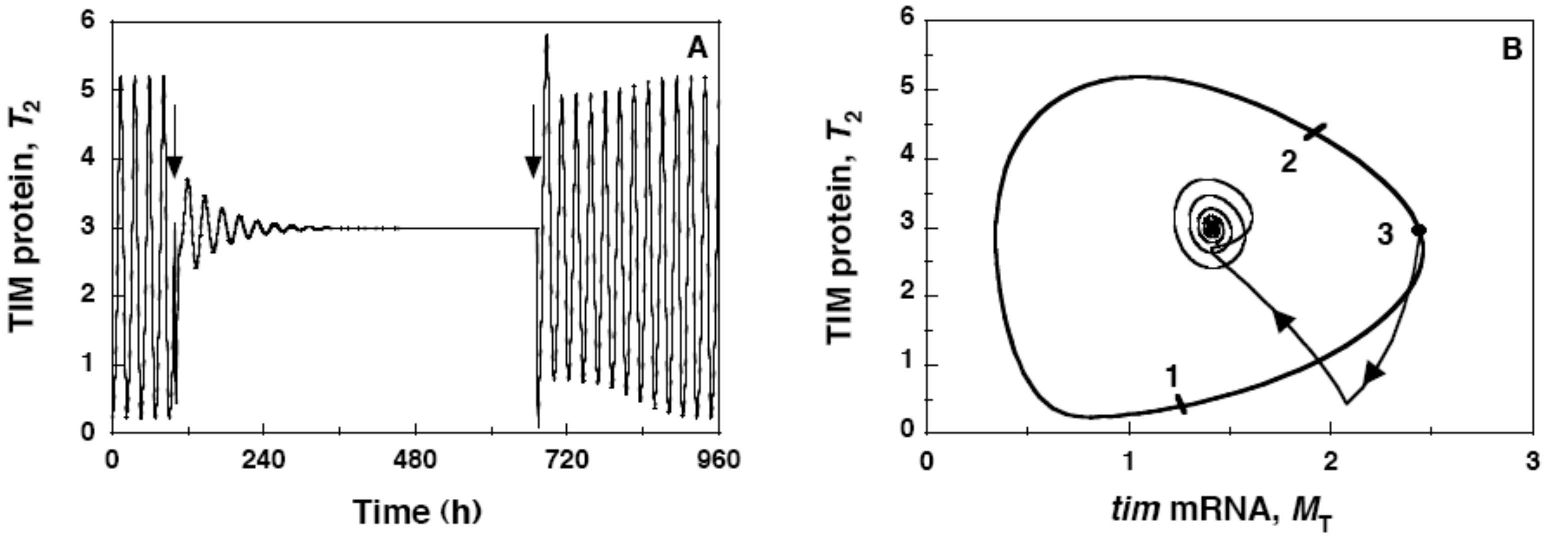




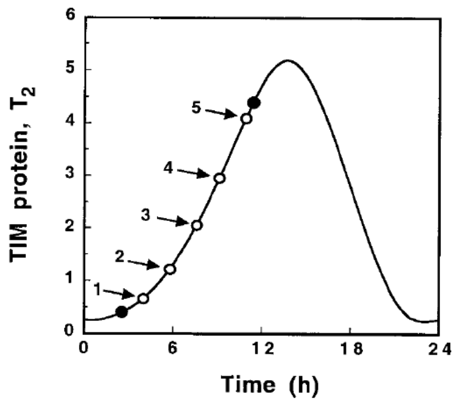
Leloup J-C & Goldbeter A (2001) A molecular explanation for the long-term suppression of circadian rhythms by a single light pulse. *Am J Physiol* **280**, R1206-12.

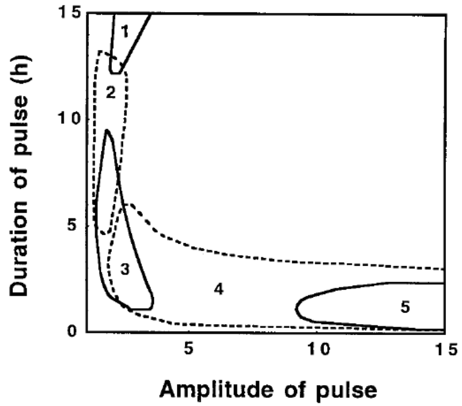
Leloup-Goldbeter's 10-variable model

Suppression of oscillations by a light pulse



A pulse of light can permanently stop the oscillations or restore the oscillations, but there are conditions on:
- phase of the pulse
- amplitude of the pulse
- duration of the pulse

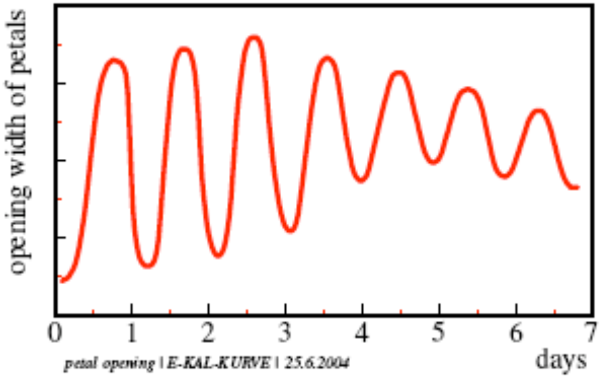




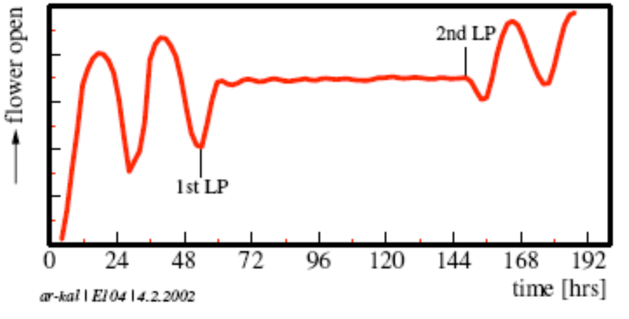
Leloup-Goldbeter's 10-variable model

Suppression of oscillations by a light pulse

Experiment in *Kalanchoe*:



circadian rhythm of leaf movement



arrest of the rhythm after a light pulse

Engelmann W and Johnsson A (1978) Attenuation of the Petal Movement Rhythm in *Kalanchoe* with Light Pulses. *Physiol Plant* 43: 68-76

Modeling circadian rhythms: summary

- The genetic basis of circadian rhythms can be modeled by ordinary differential equations.
- Because of the large number of variables and multiple sources of nonlinearities, analytical approaches are very limited and one must resort to numerical simulations (e.g. with xpp-auto).
- Simulation of the models shows that the endogenous circadian rhythm (in constant conditions) can be modeled as limit cycles oscillations.
- The light-dark cycle (LD) can be modeled by periodic modulation of the light controlled parameter. The simulations account for the entrainment of the oscillations in various LD conditions (different day lengths, different photoperiod, etc).
- The effect of mutations on the period length can be modeled by changing specific parameter values.
- Simulation can be used to provide explanation of non-intuitive observations (cf. the example of suppression of oscillations by a light pulse).