

Circadian clocks and noise



Didier Gonze

Overview



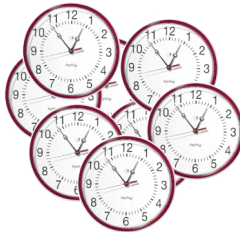
Molecular mechanism

What is the molecular mechanism underlying circadian oscillations?



Effect of noise

How robust are the circadian oscillations with respect to molecular noise?

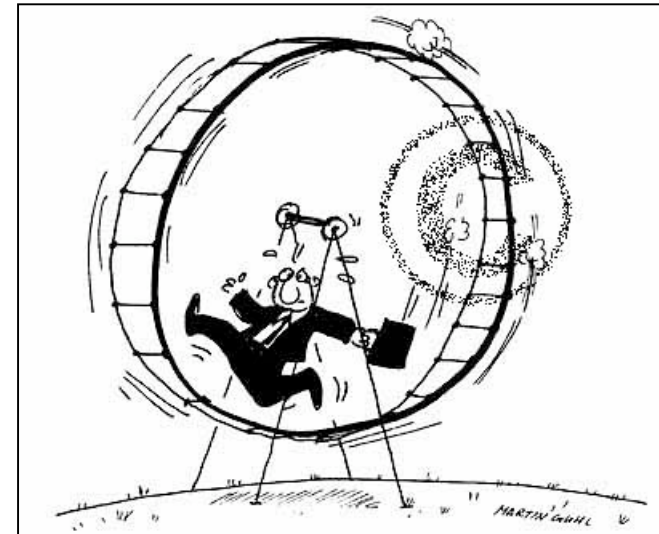
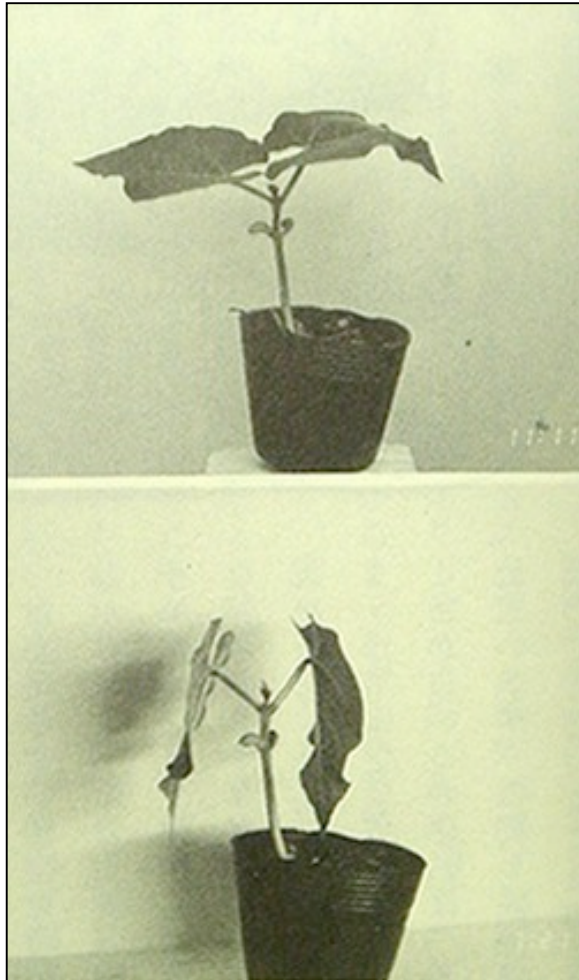


Synchronization

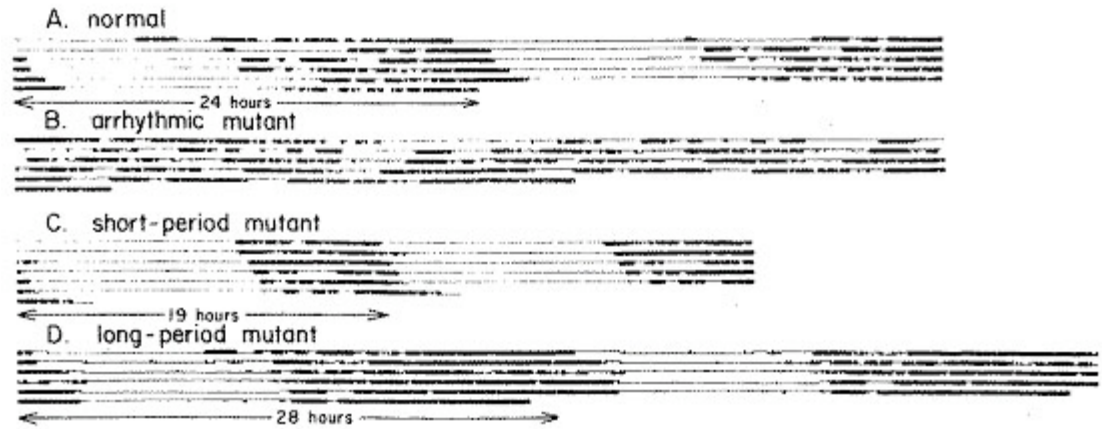
By which mechanism the circadian oscillators are synchronized?

Circadian rhythms

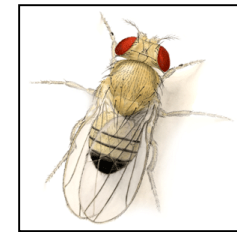
Circadian rhythms are endogenous 24h-period rhythms that allow living organisms to live in phase with the alternance of day and night.



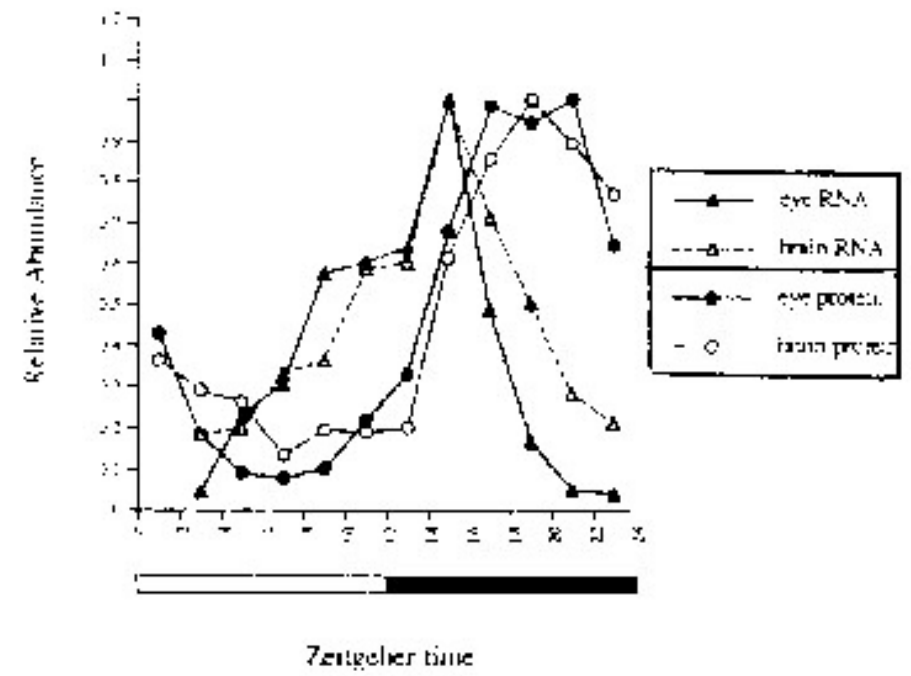
Circadian rhythms in *Drosophila*



Locomotor activity



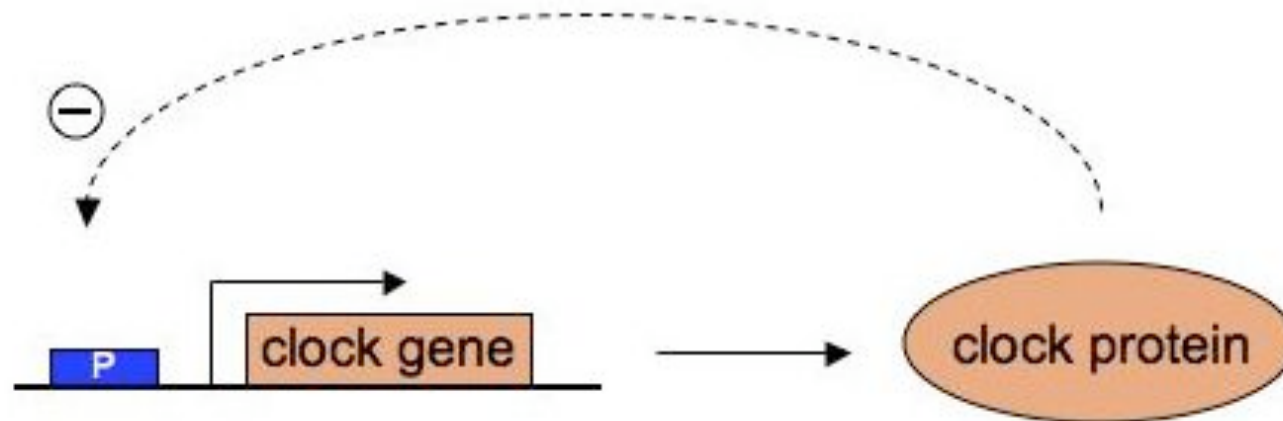
Expression of *per* gene



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

Molecular mechanism of circadian clocks

Core mechanism: negative feedback loop



clock gene

Drosophila

per (period), *tim* (timeless)

Mammals

mper1-3 (period homologs)

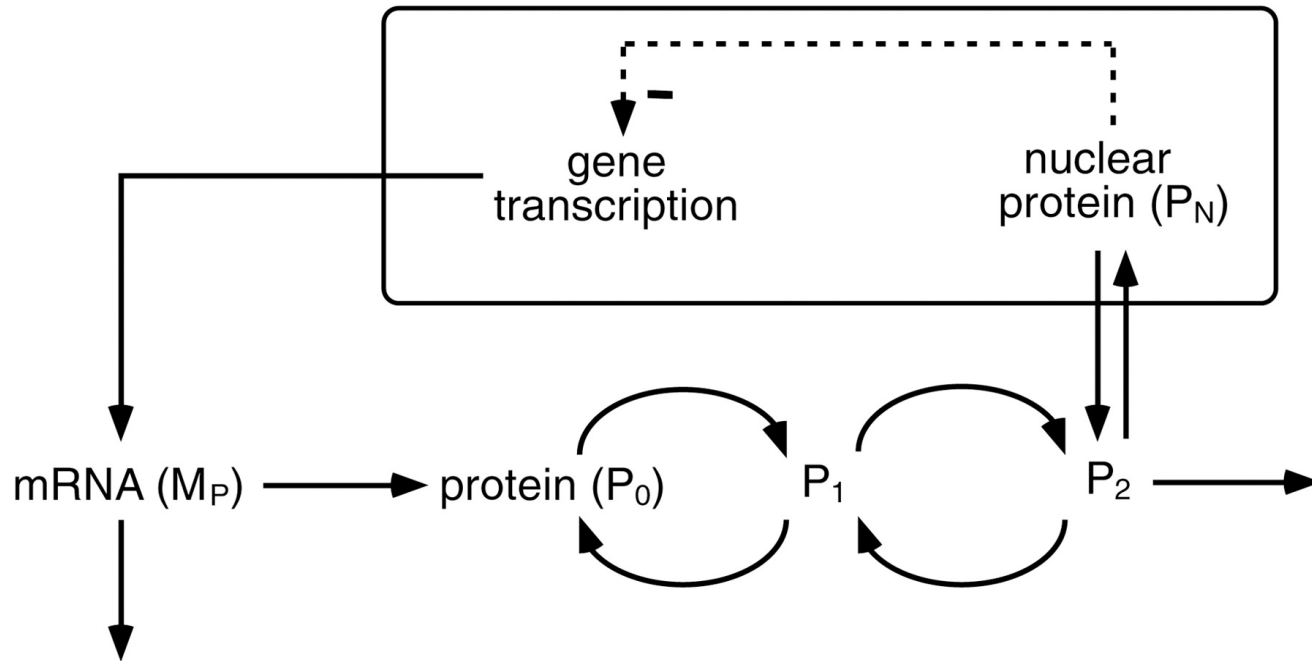
Neurospora

frq (frequency)



Deterministic models for circadian rhythms

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

$$\begin{array}{ll}
 \text{per mRNA} & \frac{dM_P}{dt} = v_s \frac{K_I^n}{K_I^n + P_N^n} - v_m \frac{M_P}{K_m + M_P} \\
 \\
 \text{PER protein} & \frac{dP_0}{dt} = k_s M_P - v_1 \frac{P_0}{K_1 + P_0} + v_2 \frac{P_1}{K_2 + P_1} \\
 \text{(unphosph.)} & \\
 \\
 \text{PER protein} & \frac{dP_1}{dt} = v_1 \frac{P_0}{K_1 + P_0} - v_2 \frac{P_1}{K_2 + P_1} - v_3 \frac{P_1}{K_3 + P_1} + v_4 \frac{P_2}{K_4 + P_2} \\
 \text{(monophosph.)} & \\
 \\
 \text{PER protein} & \frac{dP_2}{dt} = v_3 \frac{P_1}{K_3 + P_1} - v_4 \frac{P_2}{K_4 + P_2} - v_d \frac{P_2}{K_d + P_2} - k_1 P_2 + k_2 P_N \\
 \text{(biphosph.)} & \\
 \\
 \text{nuclear} & \frac{dP_N}{dt} = k_1 P_2 - k_2 P_N \\
 \text{PER protein} &
 \end{array}$$

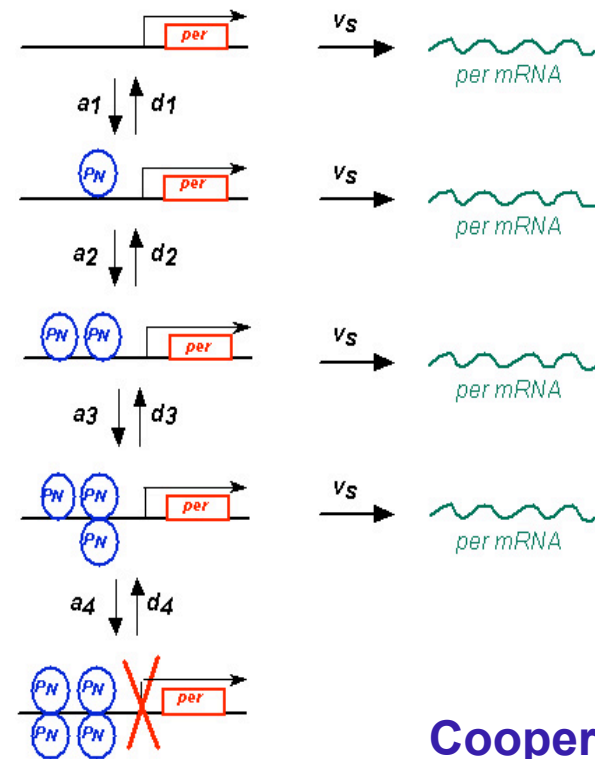
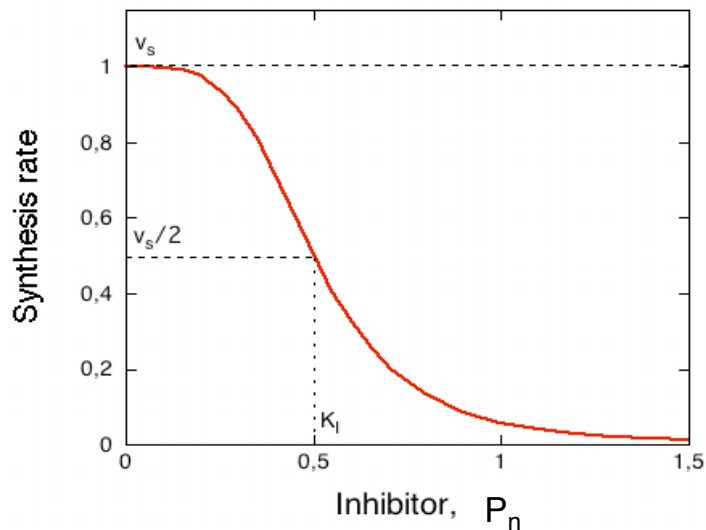
Goldbeter A (1995) A model for circadian oscillations in the *Drosophila* period protein (PER).
Proc. R. Soc. Lond. B. Biol. Sci. 261, 319-24.

Goldbeter's 5-variable model

Dynamics of *per* mRNA (M_P): synthesis

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

Inhibition: Hill function



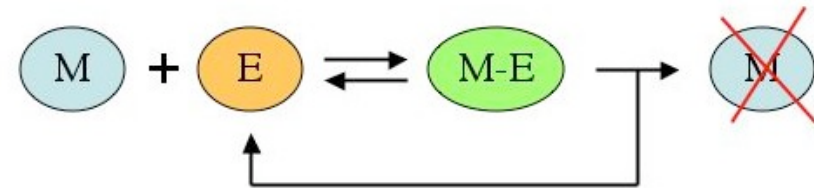
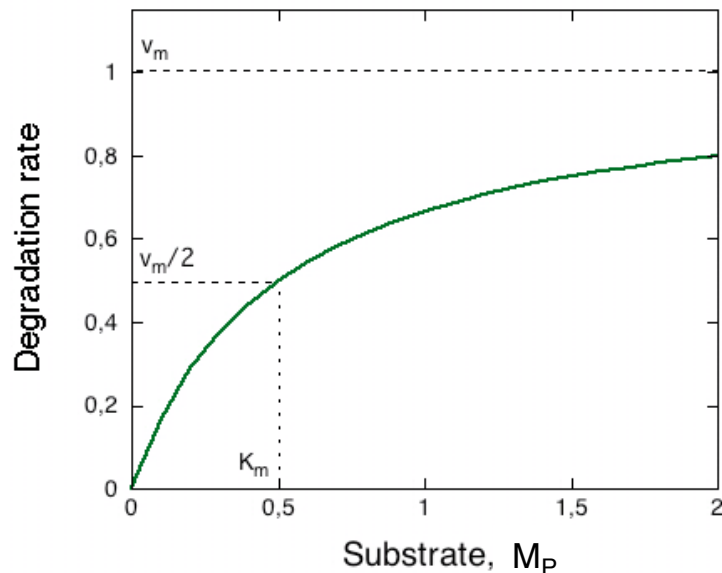
Cooperativity

Goldbeter's 5-variable model

Dynamics of *per* mRNA (M_P): degradation

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

Degradation: Michaelis-Menten



$$E \ll M$$

$$k_1, k_{-1} \gg k_2$$

$$E_{tot} = E + ME$$

$$K_M = (k_{-1} + k_2) / k_1$$

$$v_m = k_2 E_{tot}$$

Goldbeter's 5-variable model

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

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

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

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

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

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

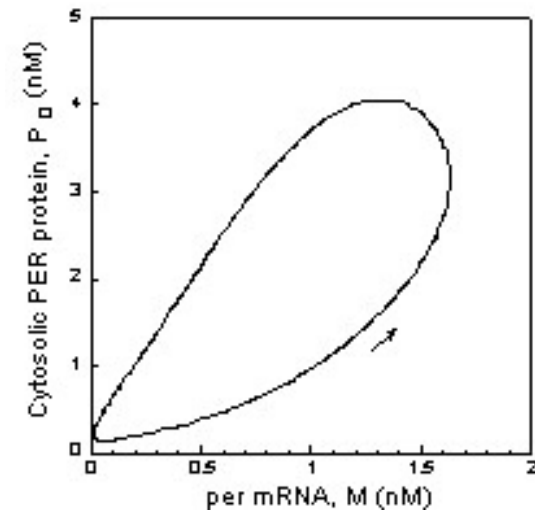
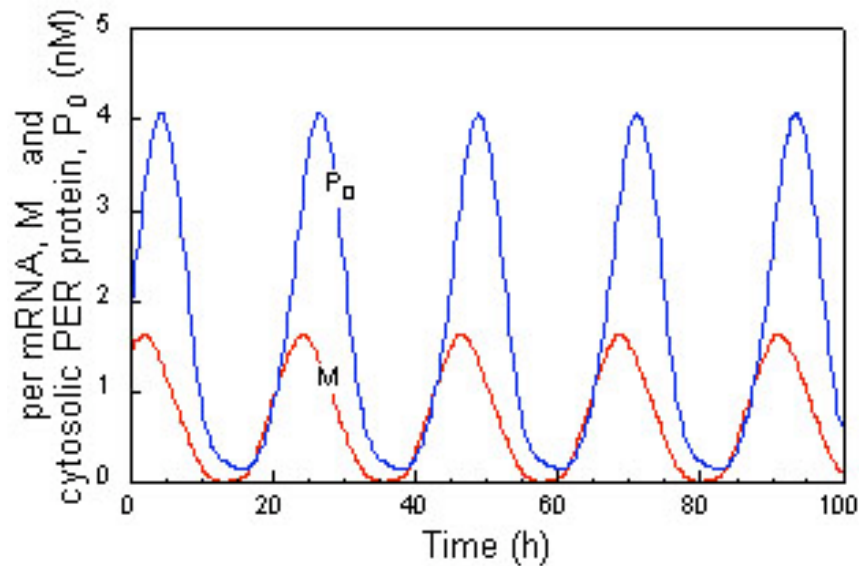
$$\frac{dP_2}{dt} = v_3 \frac{P_1}{K_3 + P_1} - v_4 \frac{P_2}{K_4 + P_2} - v_d \frac{P_2}{K_d + P_2} - \boxed{k_1 P_2 + k_2 P_N}$$

PER nuclear transport: linear

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

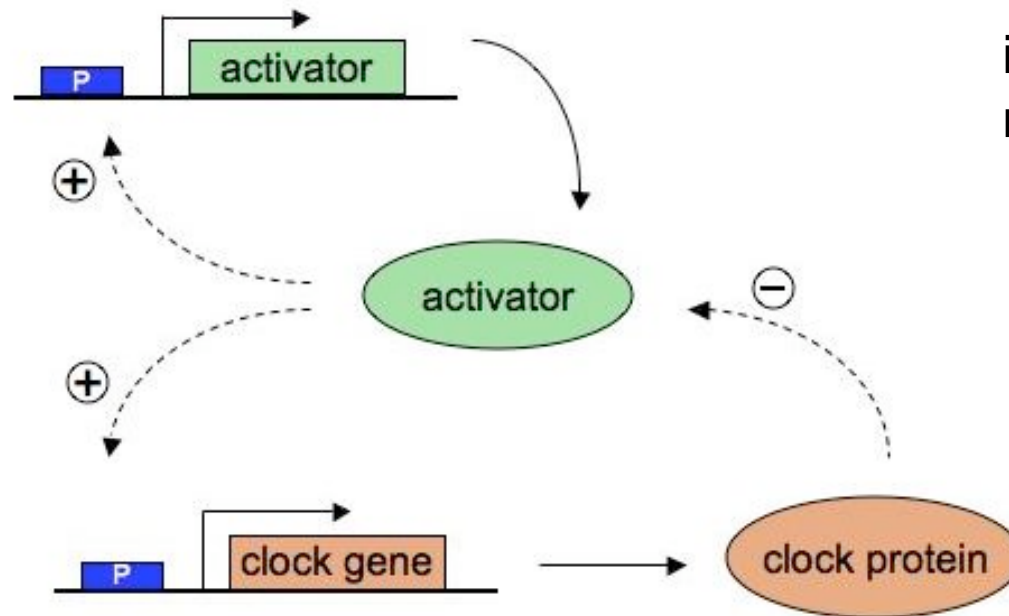
Goldbeter's 5-variable model

Limit-cycle oscillations



- Mutants (long-period, short-period, arrhythmic)
- Entrainment by light-dark cycles
- Phase shift induced by light pulses
- Suppression of oscillations by a light pulse
- Temperature compensation
- ...

Molecular mechanism of circadian clocks



interlocked positive and negative feedback loops

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

Example: circadian clock in mammals

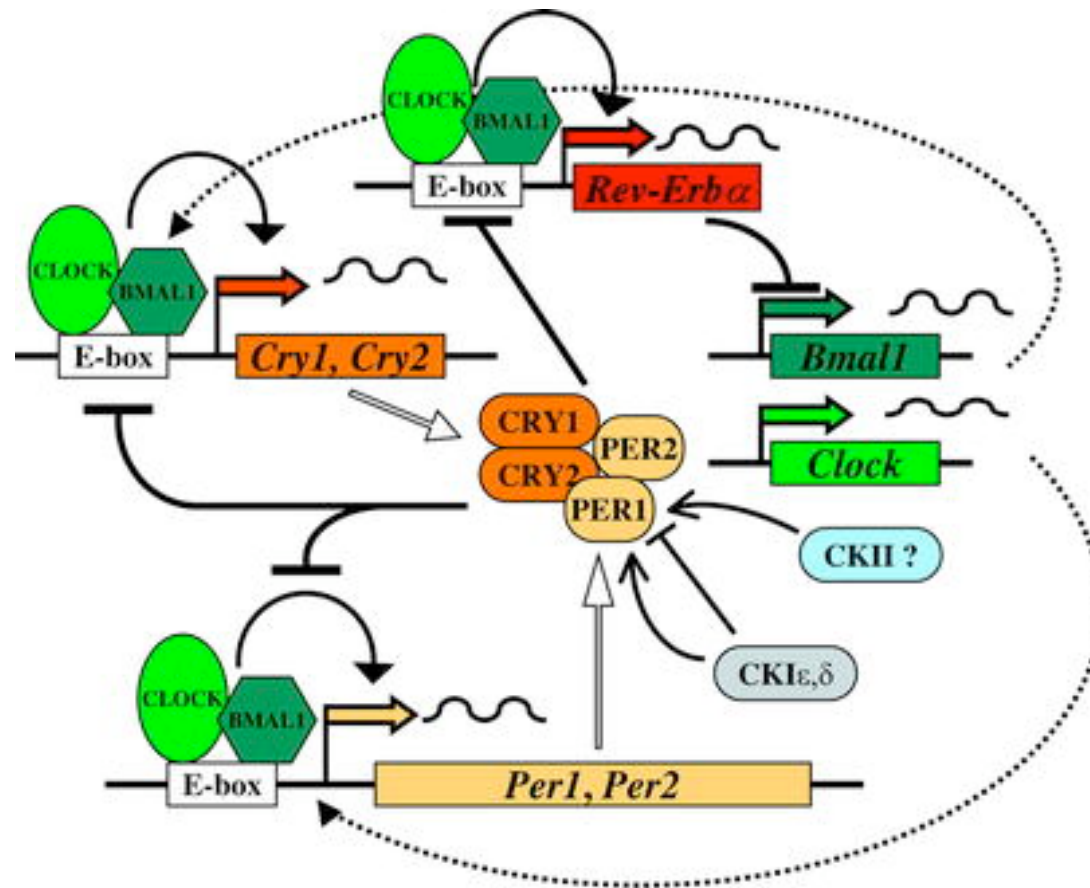
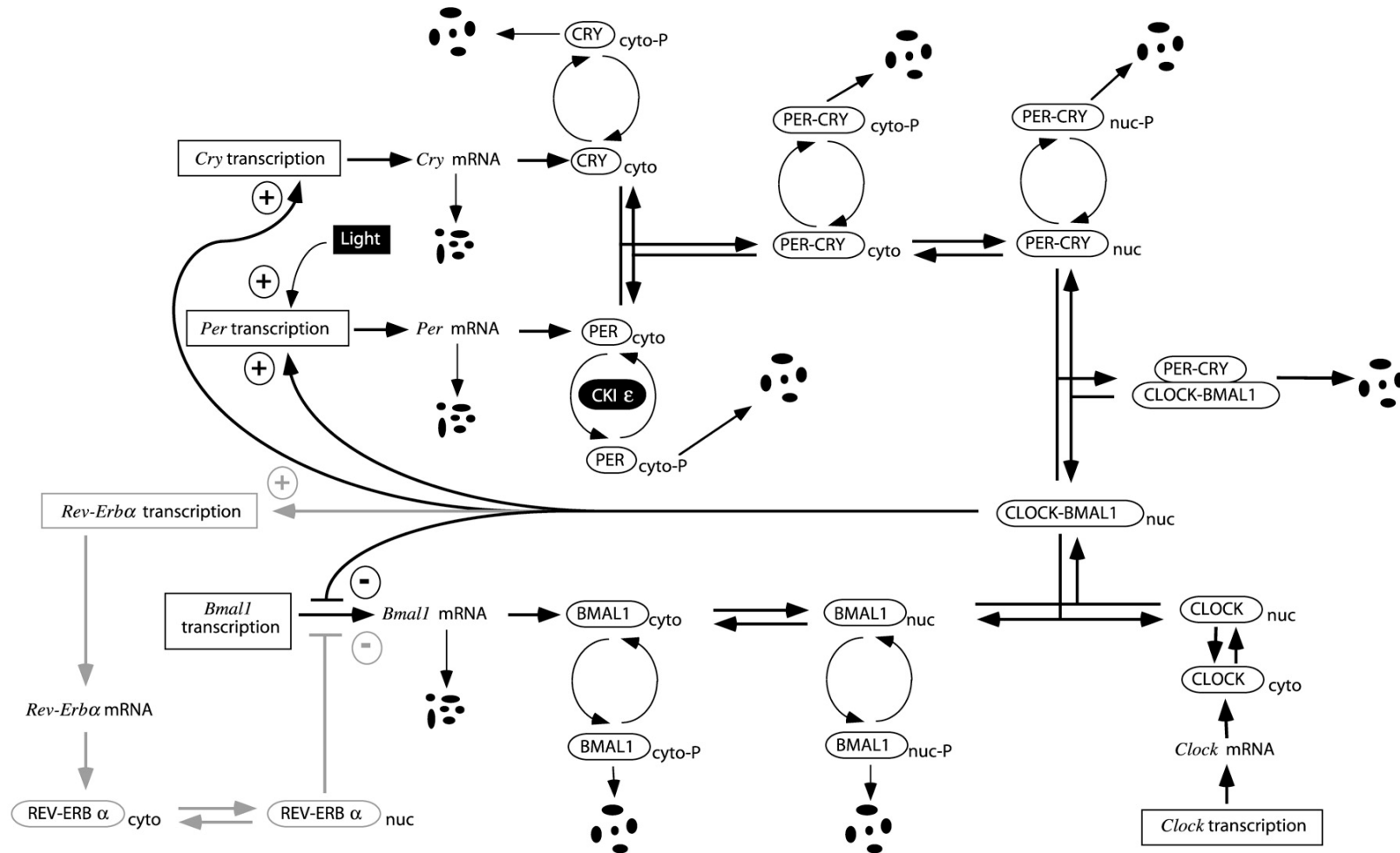


Figure from Gachon, Nagoshi, Brown, Ripperger, Schibler (2004) The mammalian circadian timing system: from gene expression to physiology. *Chromosoma* **113**: 103-112.

Model for the 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.

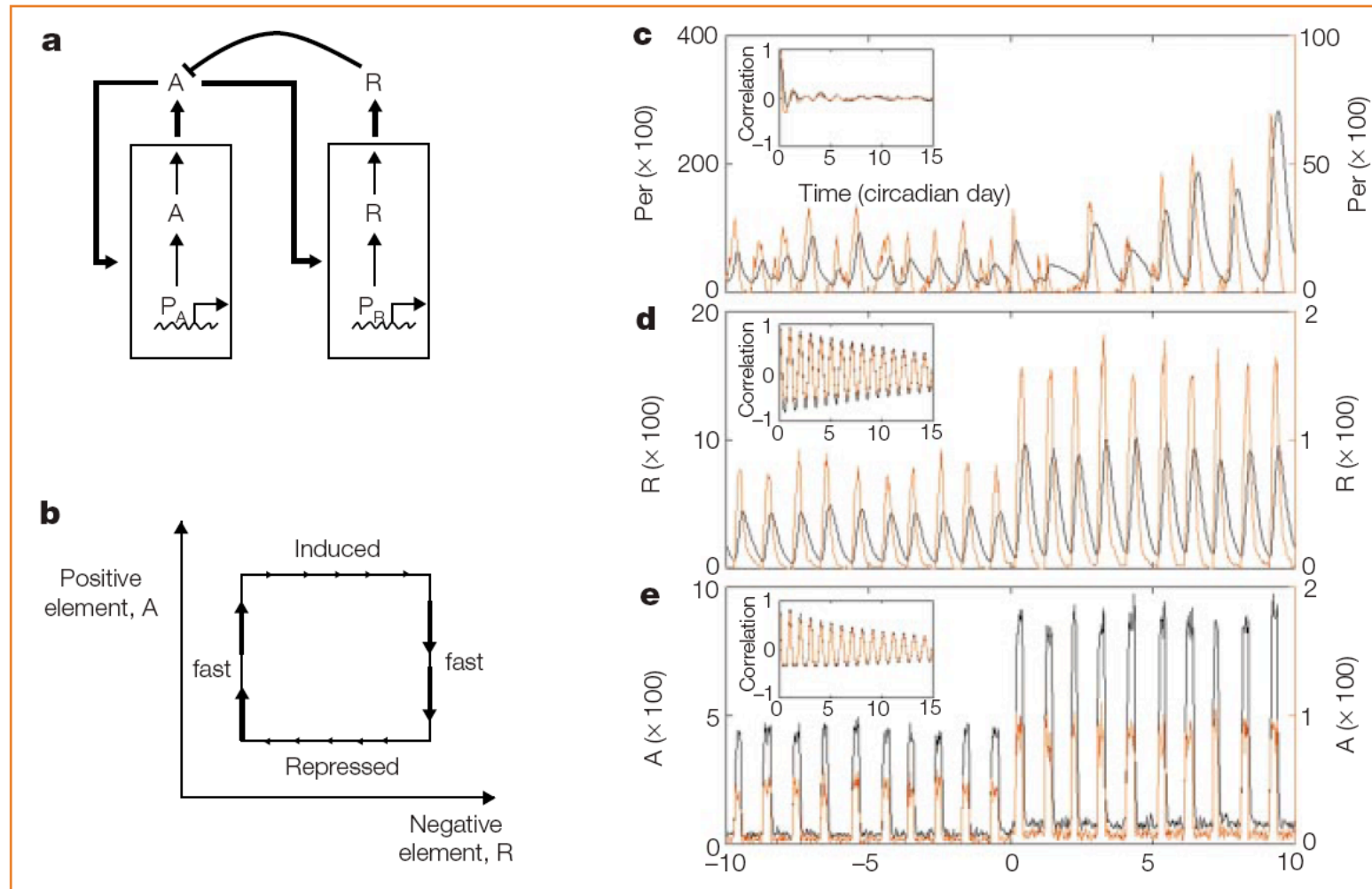


Stochastic models for circadian rhythms

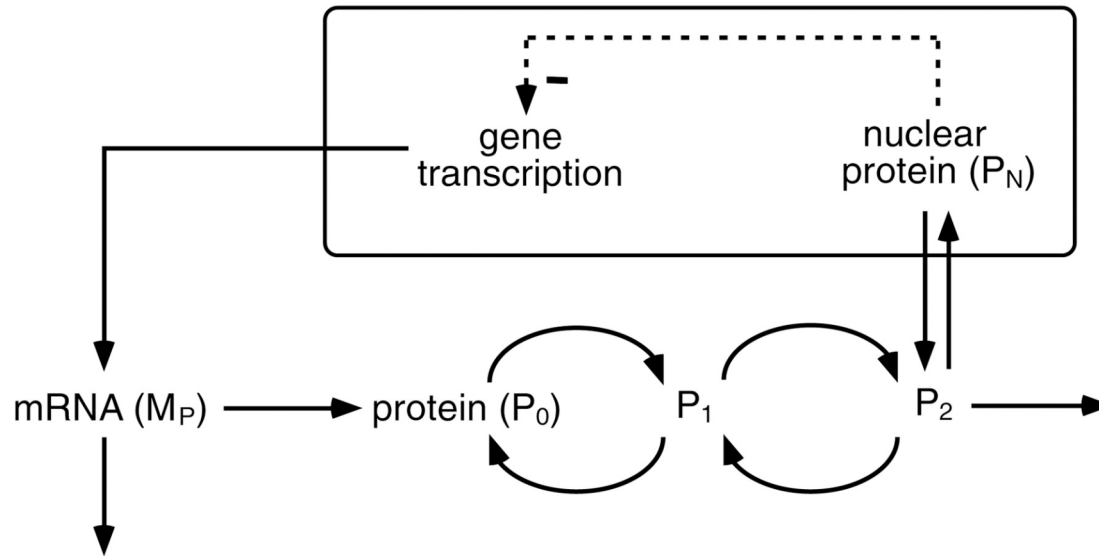
Circadian clocks limited by noise ?

Circadian clocks limited by noise

N. Barkai & S. Leibler, *Nature* (2000) 403: 267-268



Goldbeter's 5-variable model



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

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

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

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

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

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

Stochastic simulations

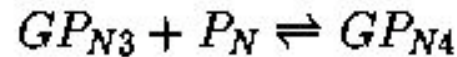
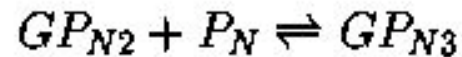
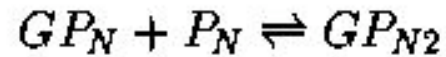
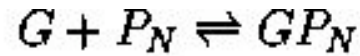
Fluctuations are due the limited number of molecules (**molecular noise**). They can be assessed thanks to stochastic simulations.

Such an approach requires a description in term of the number of molecules (instead of concentrations).

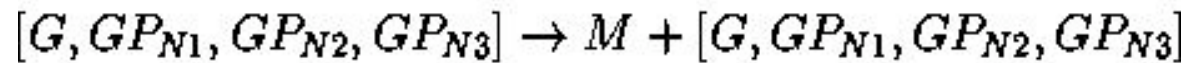
Here, we will focus on several robustness factors:

- Number of molecules
- Degree of cooperativity
- Periodic forcing (LD cycle)
- Proximity of a bifurcation point
- Coupling between cells

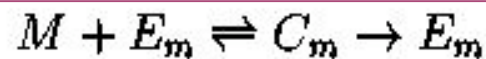
Detailed reaction scheme



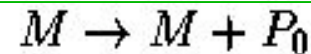
Successive binding of 4 P_N molecules to the gene G



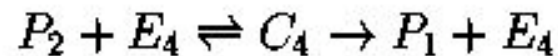
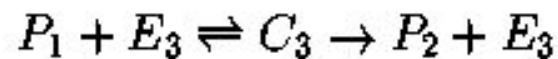
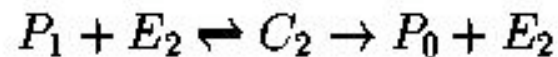
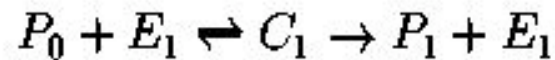
Transcription



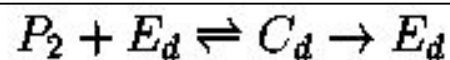
Degradation of mRNA



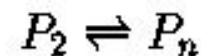
Translation



Phosphorylation /
Dephosphorylation



Degradation of protein



Translocation of protein

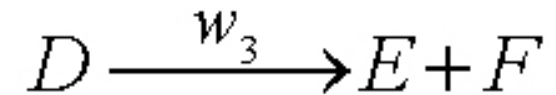
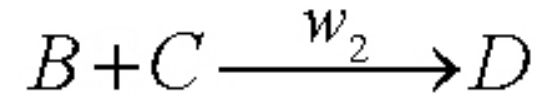
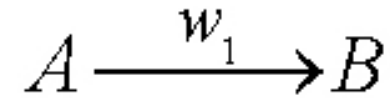
Gillespie algorithm

A **reaction rate** w_i is associated to each reaction step. These probabilities are related to the kinetics constants.

Initial number of molecules of each species are specified.

The **time interval** is computed stochastically according the reaction rates.

At each time interval, the **reaction** that occurs is chosen randomly according to the probabilities w_i and both the number of molecules and the reaction rates are updated.



...

Gillespie D.T. (1977) Exact stochastic simulation of coupled chemical reactions. *J. Phys. Chem.* 81: 2340-2361.

Gillespie D.T., (1976) A General Method for Numerically Simulating the Stochastic Time Evolution of Coupled Chemical Reactions. *J. Comp. Phys.*, 22: 403-434.

Stochastic description of the model

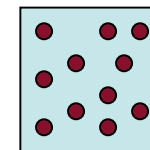
Reaction number	Reaction step	Probability of reaction
1	$G + P_N \xrightarrow{u_1} GP_N$	$w_1 = a_1 \times G \times P_N / \Omega$
2	$GP_N \xrightarrow{d_1} G + P_N$	$w_2 = d_1 \times GP_N$
3	$GP_N + P_N \xrightarrow{u_2} GP_{N2}$	$w_3 = a_2 \times GP_N \times P_N / \Omega$
4	$GP_{N2} \xrightarrow{d_2} GP_N + P_N$	$w_4 = d_2 \times GP_{N2}$
5	$GP_{N2} + P_N \xrightarrow{u_3} GP_{N3}$	$w_5 = a_3 \times GP_{N2} \times P_N / \Omega$
6	$GP_{N3} \xrightarrow{d_3} GP_{N2} + P_N$	$w_6 = d_3 \times GP_{N3}$
7	$GP_{N3} + P_N \xrightarrow{u_4} GP_{N4}$	$w_7 = a_4 \times GP_{N3} \times P_N / \Omega$
8	$GP_{N4} \xrightarrow{d_4} GP_{N3} + P_N$	$w_8 = d_4 \times GP_{N4}$
9	$[G, GP_N, GP_{N2}, GP_{N3}] \xrightarrow{v_s} M_P$	$w_9 = v_s \times (G + GP_N + GP_{N2} + GP_{N3})$
10	$M_P + E_m \xrightarrow{k_{m1}} C_m$	$w_{10} = k_{m1} \times M_P \times E_m / \Omega$
11	$C_m \xrightarrow{k_{m2}} M_P + E_m$	$w_{11} = k_{m2} \times C_m$
12	$C_m \xrightarrow{k_{m3}} E_m$	$w_{12} = k_{m3} \times C_m$
13	$M_P \xrightarrow{k_s} M_P + P_0$	$w_{13} = k_s \times M_P$
14	$P_0 + E_1 \xrightarrow{k_{11}} C_1$	$w_{14} = k_{11} \times P_0 \times E_1 / \Omega$
15	$C_1 \xrightarrow{k_{12}} P_0 + E_1$	$w_{15} = k_{12} \times C_1$
16	$C_1 \xrightarrow{k_{13}} P_1 + E_1$	$w_{16} = k_{13} \times C_1$
17	$P_1 + E_2 \xrightarrow{k_{21}} C_2$	$w_{17} = k_{21} \times P_1 \times E_2 / \Omega$
18	$C_2 \xrightarrow{k_{22}} P_1 + E_2$	$w_{18} = k_{22} \times C_2$
19	$C_2 \xrightarrow{k_{23}} P_0 + E_2$	$w_{19} = k_{23} \times C_2$
20	$P_1 + E_3 \xrightarrow{k_{31}} C_3$	$w_{20} = k_{31} \times P_1 \times E_3 / \Omega$
21	$C_3 \xrightarrow{k_{32}} P_1 + E_3$	$w_{21} = k_{32} \times C_3$
22	$C_3 \xrightarrow{k_{33}} P_2 + E_3$	$w_{22} = k_{33} \times C_3$
23	$P_2 + E_4 \xrightarrow{k_{41}} C_4$	$w_{23} = k_{41} \times P_2 \times E_4 / \Omega$
24	$C_4 \xrightarrow{k_{42}} P_2 + E_4$	$w_{24} = k_{42} \times C_4$
25	$C_4 \xrightarrow{k_{43}} P_1 + E_4$	$w_{25} = k_{43} \times C_4$
26	$P_2 + E_d \xrightarrow{k_{d1}} C_d$	$w_{26} = k_{d1} \times P_2 \times E_d / \Omega$
27	$C_d \xrightarrow{k_{d2}} P_2 + E_d$	$w_{27} = k_{d2} \times C_d$
28	$C_d \xrightarrow{k_{d3}} E_d$	$w_{28} = k_{d3} \times C_d$
29	$P_2 \xrightarrow{k_1} P_N$	$w_{29} = k_1 \times P_2$
30	$P_N \xrightarrow{k_2} P_2$	$w_{30} = k_2 \times P_N$

Parameter Ω (volume)



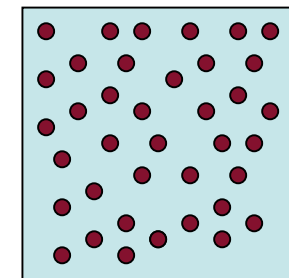
Number of molecules

Ω small



Small number of molecules, high noise

Ω large

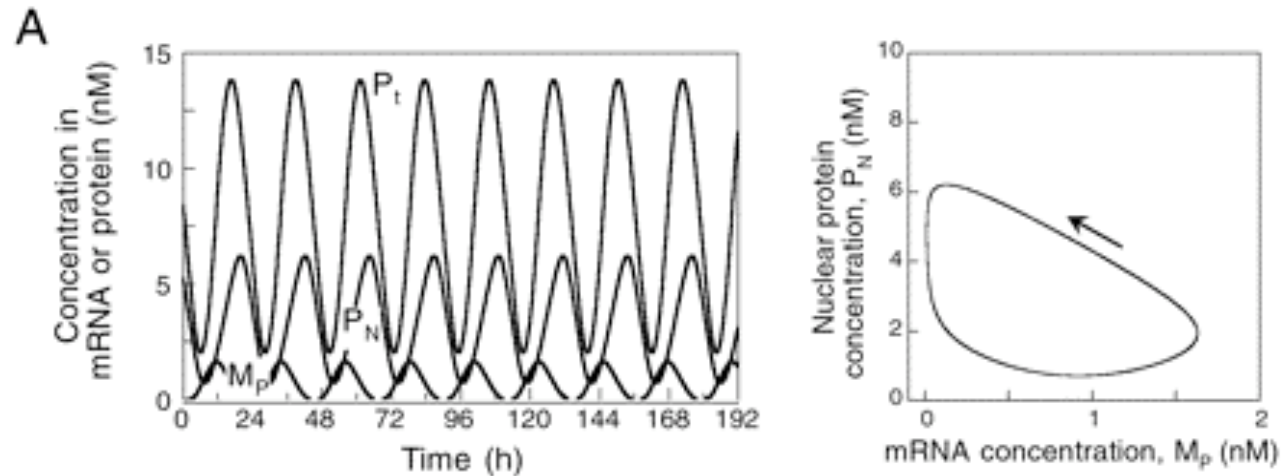


Large number of molecules, low noise

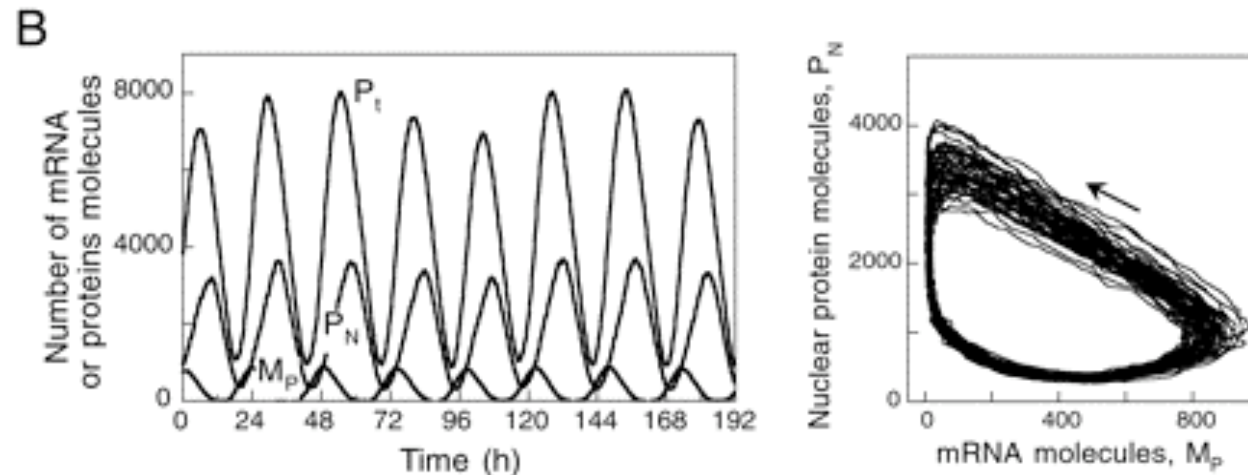
Same concentration

Stochastic oscillations and limit cycle

Deterministic



Stochastic



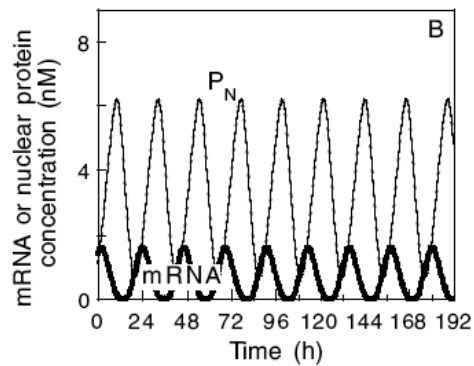
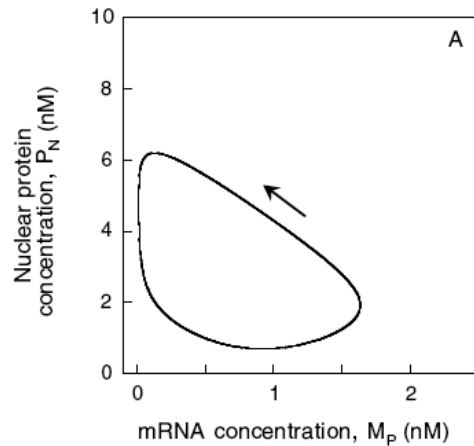
Gonze D, Halloy J, Goldbeter A (2002) Robustness of circadian rhythms with respect to molecular noise. *Proc. Natl. Acad. Sci. USA* 99: 673-678.

Developed vs non-developed model

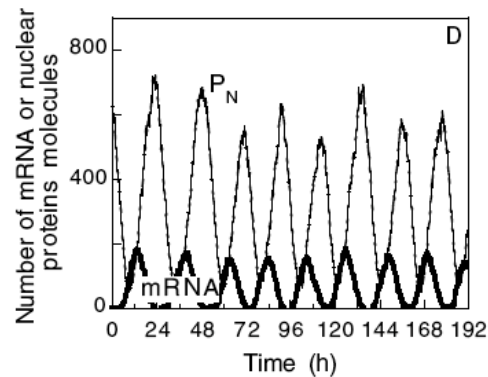
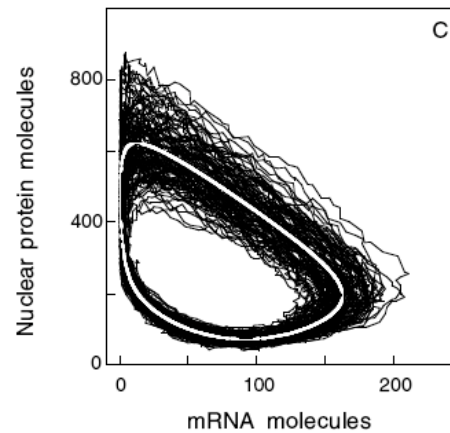
Reaction number	Reaction	Probability of reaction	Transition
1	$G \rightarrow M_P + G$	$w_1 = (v_s \Omega) \frac{(K_I \Omega)^n}{(K_I \Omega)^n + P_N^n}$	$M_P \rightarrow M_P + 1$
2	$M_P \rightarrow$	$w_3 = (v_m \Omega) \frac{M_P}{(K_m \Omega) + M_P}$	$M_P \rightarrow M_P - 1$
3	$M_P \rightarrow P_0 + M_P$	$w_2 = k_s M_P$	$P_0 \rightarrow P_0 + 1$
4	$P_0 \rightarrow P_1$	$w_4 = (v_1 \Omega) \frac{P_0}{(K_1 \Omega) + P_0}$	$P_0 \rightarrow P_0 - 1$ $P_1 \rightarrow P_1 + 1$
5	$P_1 \rightarrow P_0$	$w_5 = (v_2 \Omega) \frac{P_1}{(K_2 \Omega) + P_1}$	$P_0 \rightarrow P_0 + 1$ $P_1 \rightarrow P_1 - 1$
6	$P_1 \rightarrow P_2$	$w_6 = (v_3 \Omega) \frac{P_1}{(K_3 \Omega) + P_1}$	$P_1 \rightarrow P_1 - 1$ $P_2 \rightarrow P_2 + 1$
7	$P_2 \rightarrow P_1$	$w_7 = (v_4 \Omega) \frac{P_2}{(K_4 \Omega) + P_2}$	$P_1 \rightarrow P_1 + 1$ $P_2 \rightarrow P_2 - 1$
8	$P_2 \rightarrow$	$w_8 = (v_d \Omega) \frac{P_2}{(K_d \Omega) + P_2}$	$P_2 \rightarrow P_2 - 1$
9	$P_2 \rightarrow P_N$	$w_9 = k_1 P_2$	$P_2 \rightarrow P_2 - 1$ $P_N \rightarrow P_N + 1$
10	$P_N \rightarrow P_2$	$w_{10} = k_2 P_N$	$P_2 \rightarrow P_2 + 1$ $P_N \rightarrow P_N - 1$

Developed vs non-developed model

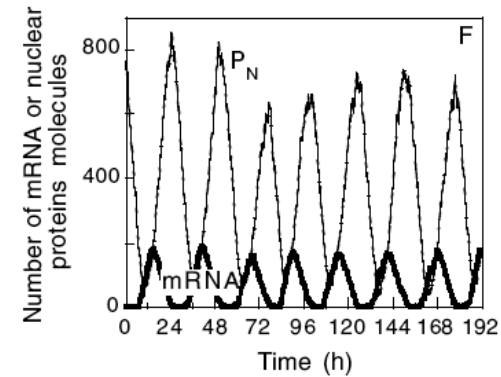
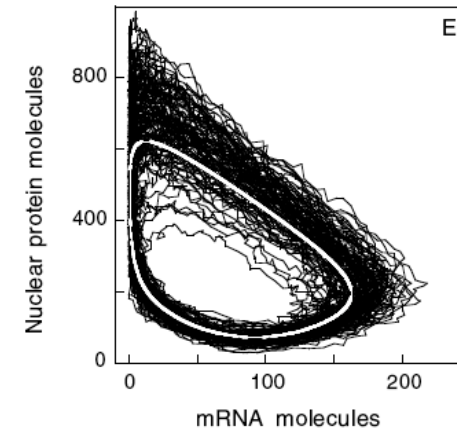
deterministic model



non-developed model
(Michaelis, Hill functions)



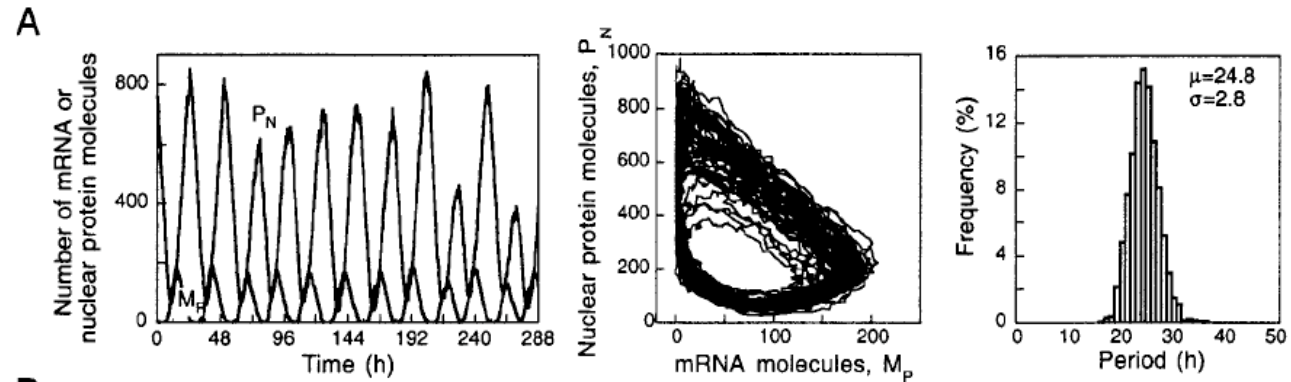
developed model
(elementary steps)



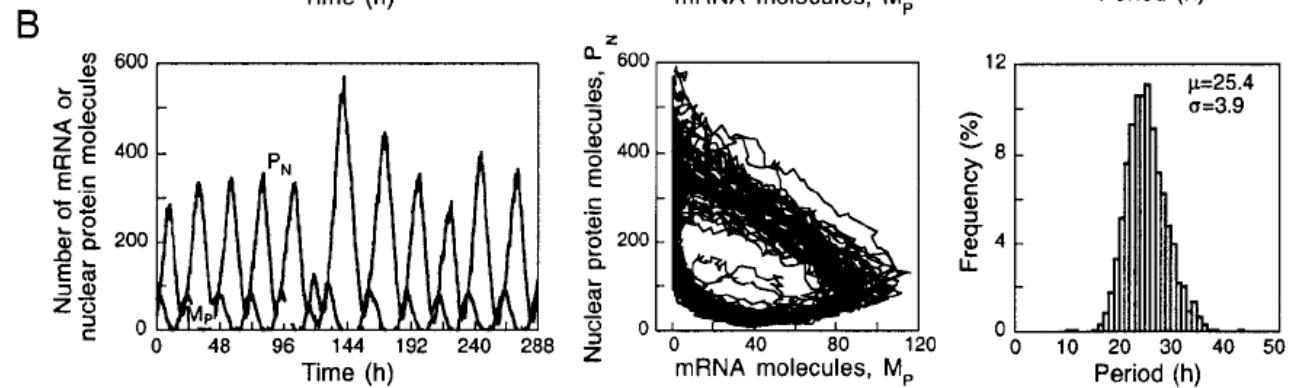
Gonze D, Halloy J, Goldbeter A (2002) Deterministic versus stochastic models for circadian rhythms. *J. Biol. Phys.* 28: 637-653.

Effect of the number of molecules, Ω

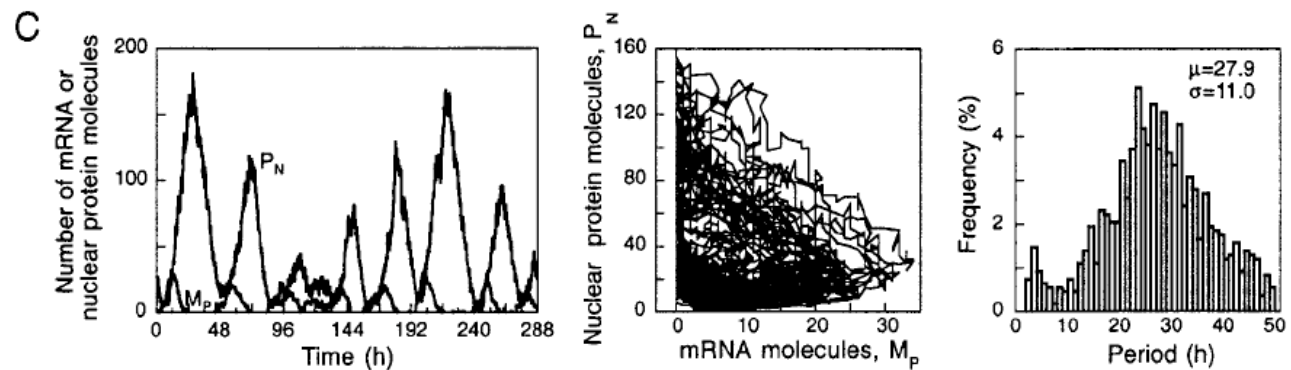
$\Omega=100$



$\Omega=50$

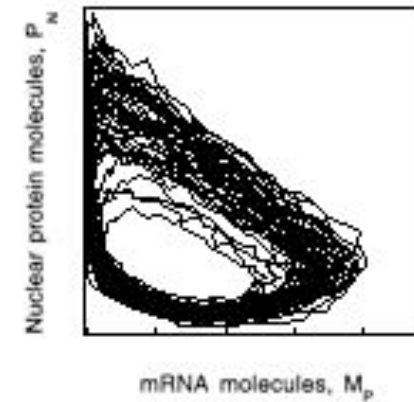
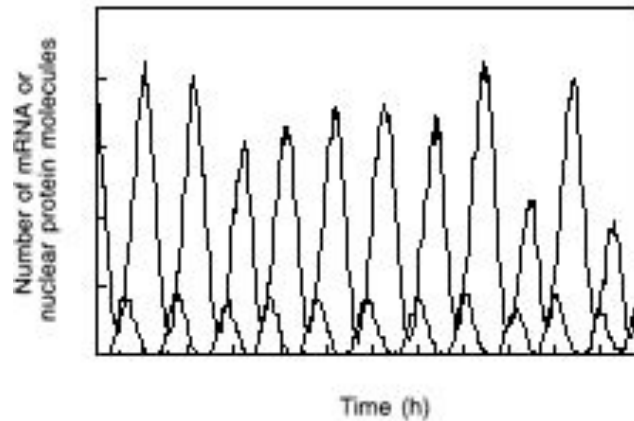


$\Omega=10$

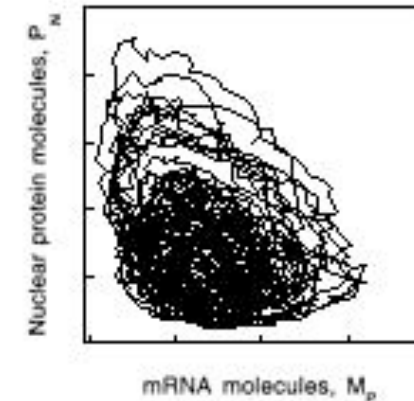
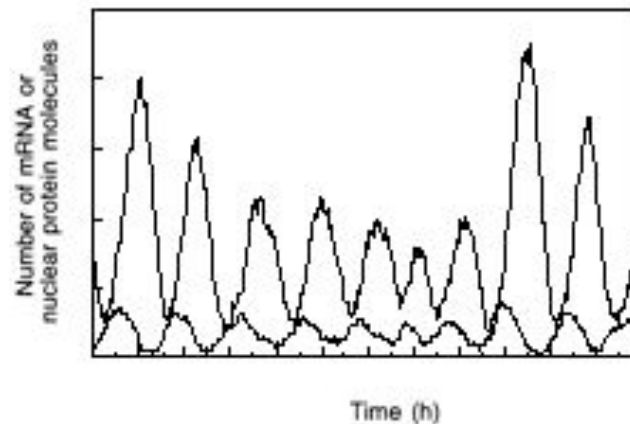


Effect of the degree of cooperativity, n

$n = 4$



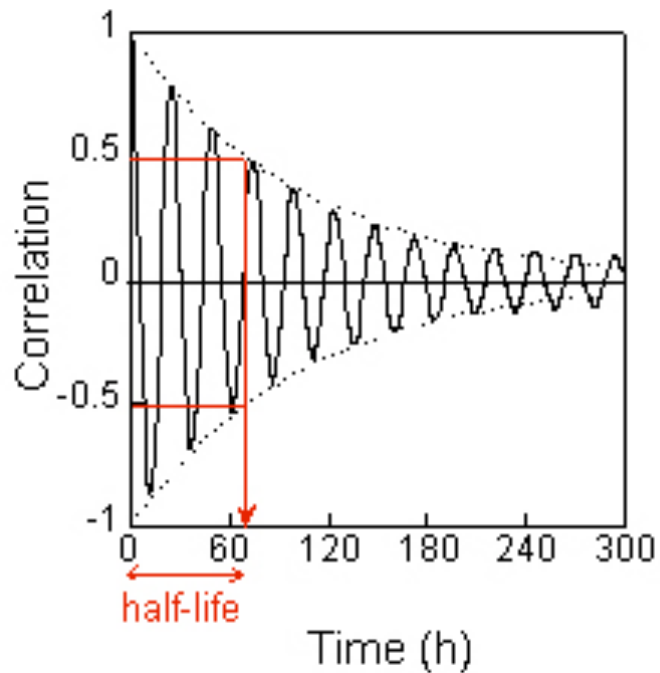
$n = 1$



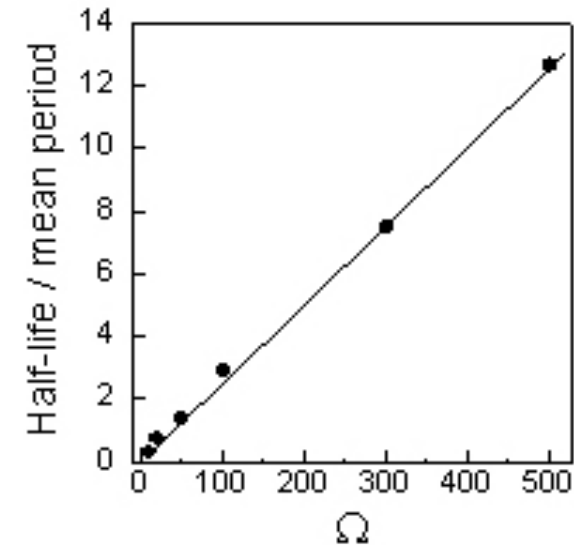
Gonze D, Halloy J, Goldbeter A (2002) Robustness of circadian rhythms with respect to molecular noise. *Proc. Natl. Acad. Sci. USA* 99: 673-678.

Quantification of the effect of noise

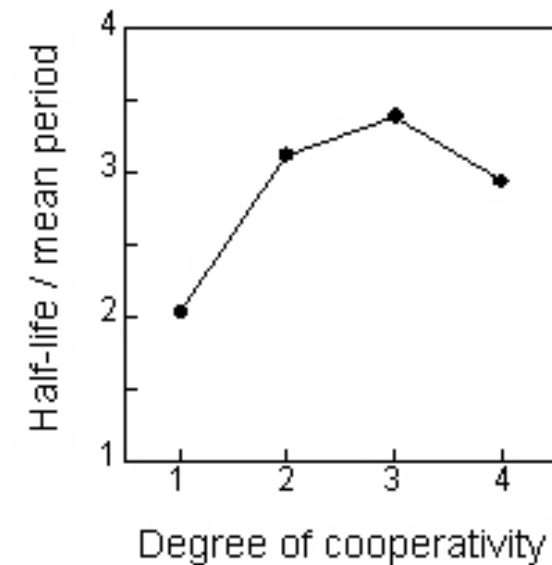
Auto-correlation function



Effect of the number of molecules, Ω



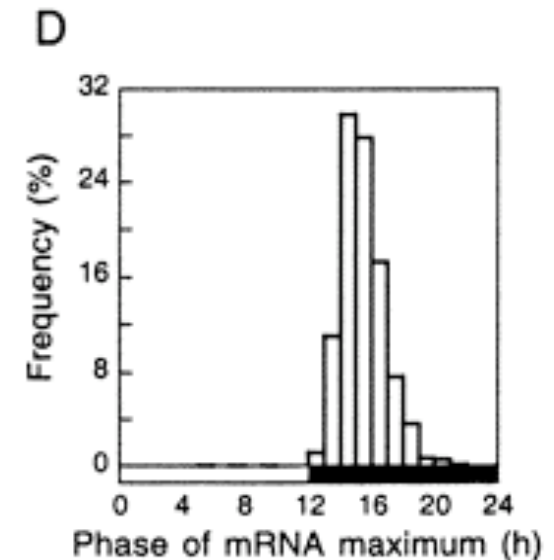
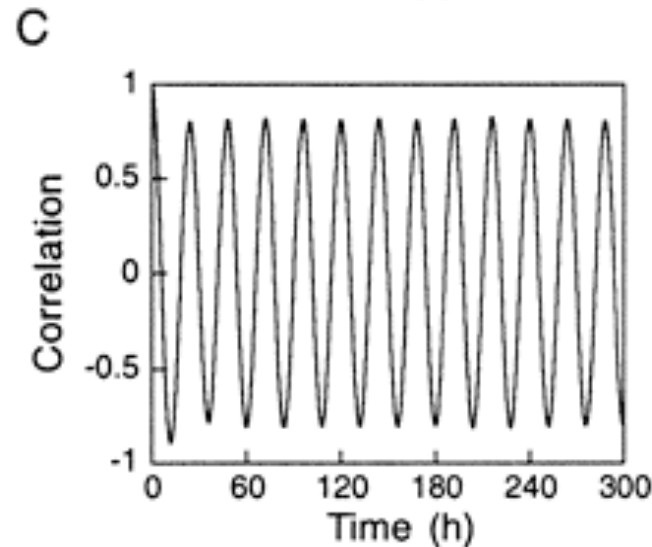
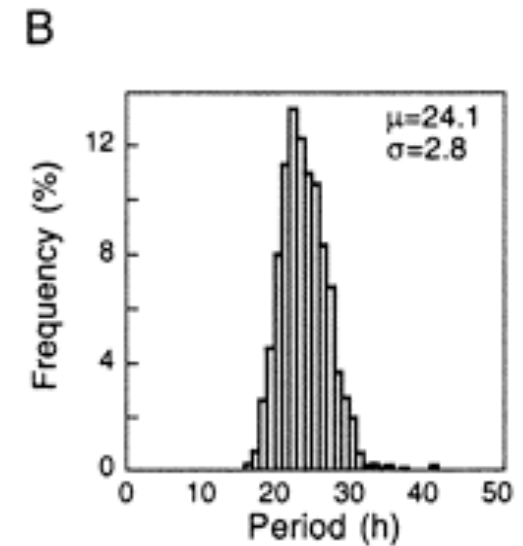
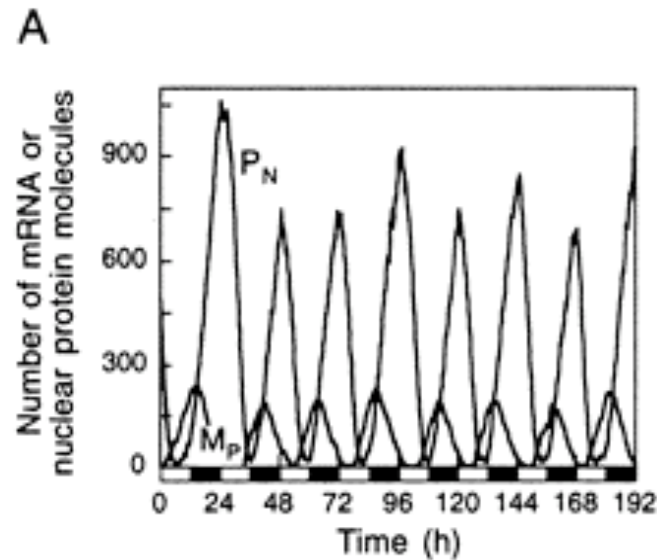
Effect of the degree of cooperativity, n



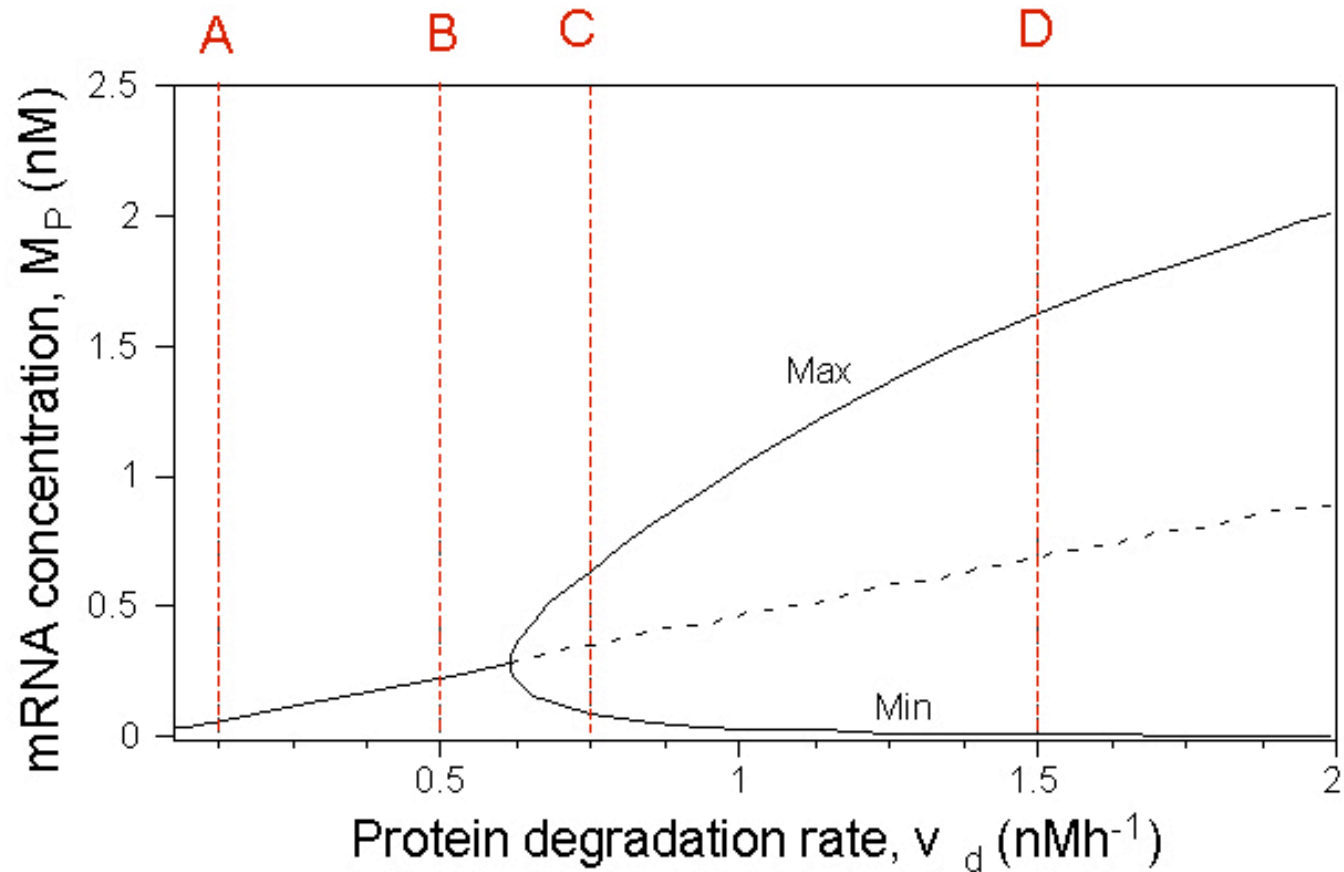
Effect of a periodic forcing (LD cycle)

Light-dark cycle
LD 12:12

light induces
PER protein
degradation, v_d

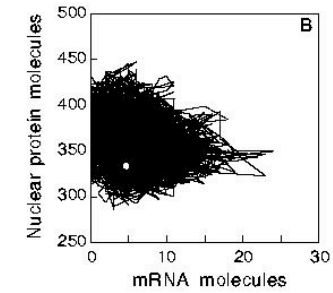
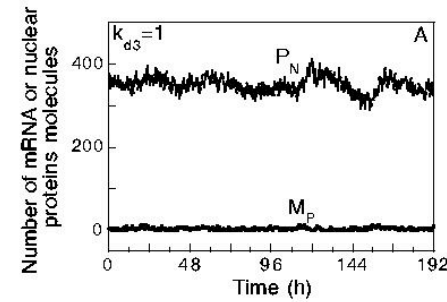
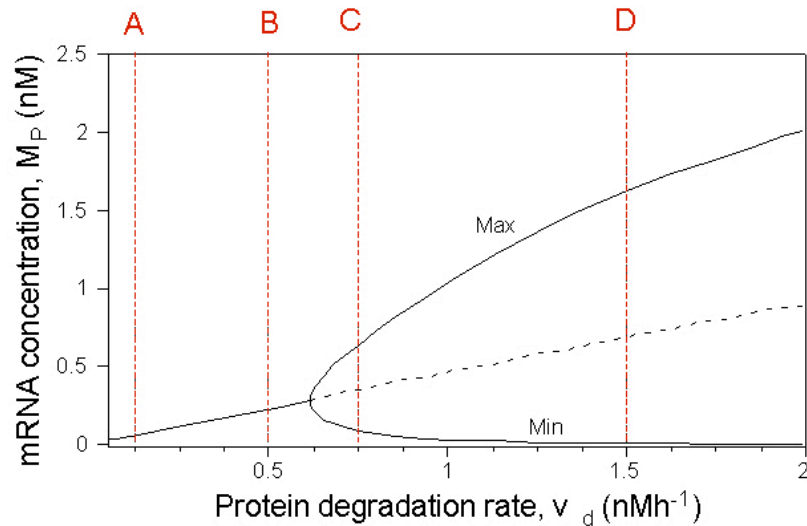


Effect of the proximity of a bifurcation point

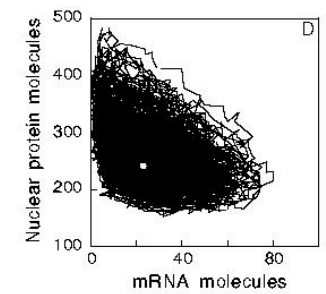
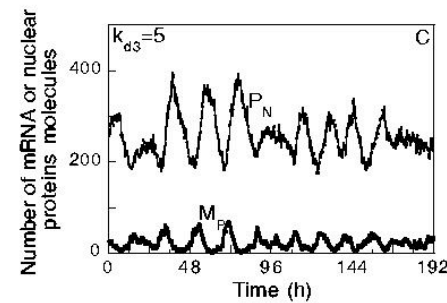


Gonze D, Halloy J, Goldbeter A (2002) Deterministic versus stochastic models for circadian rhythms. *J. Biol. Phys.* 28: 637-653.

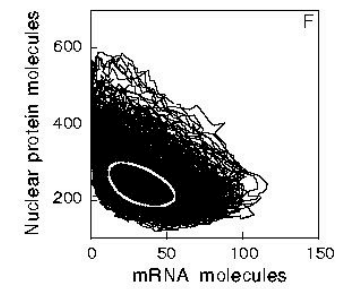
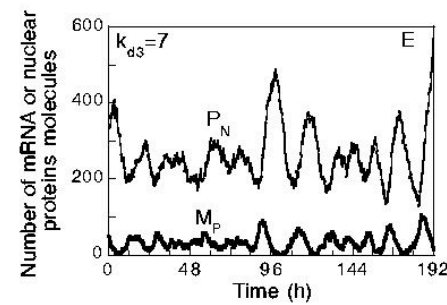
Effect of the proximity of a bifurcation point



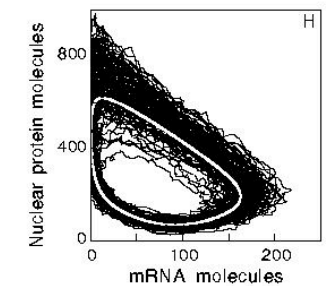
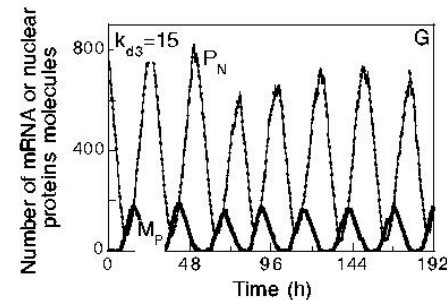
A



B

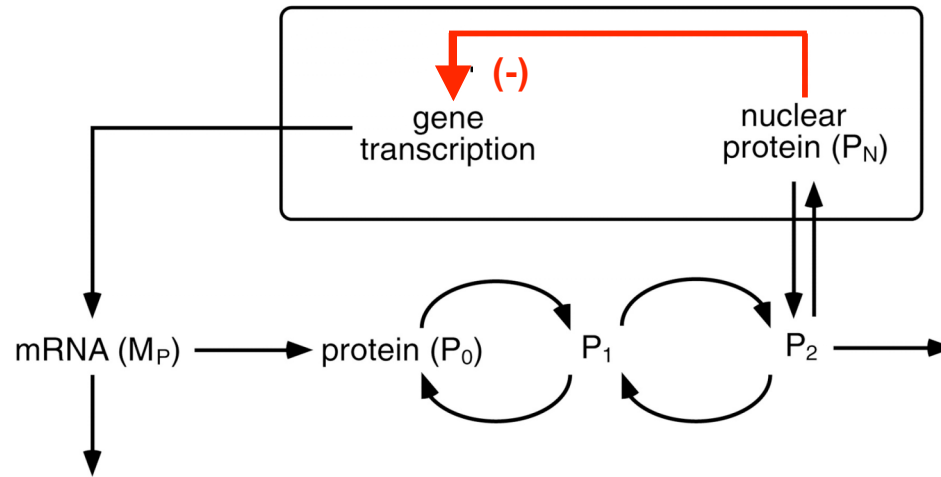


C



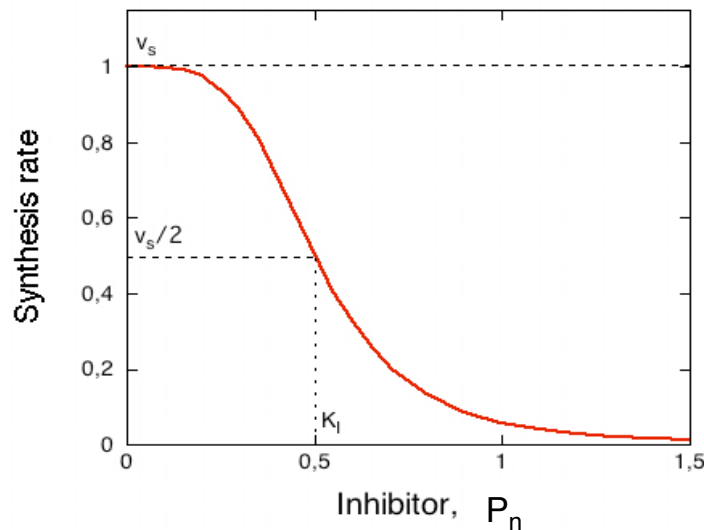
D

Cooperative protein-DNA binding



Hill function

$$v_s \frac{K_I^n}{K_I^n + P_N^n}$$



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

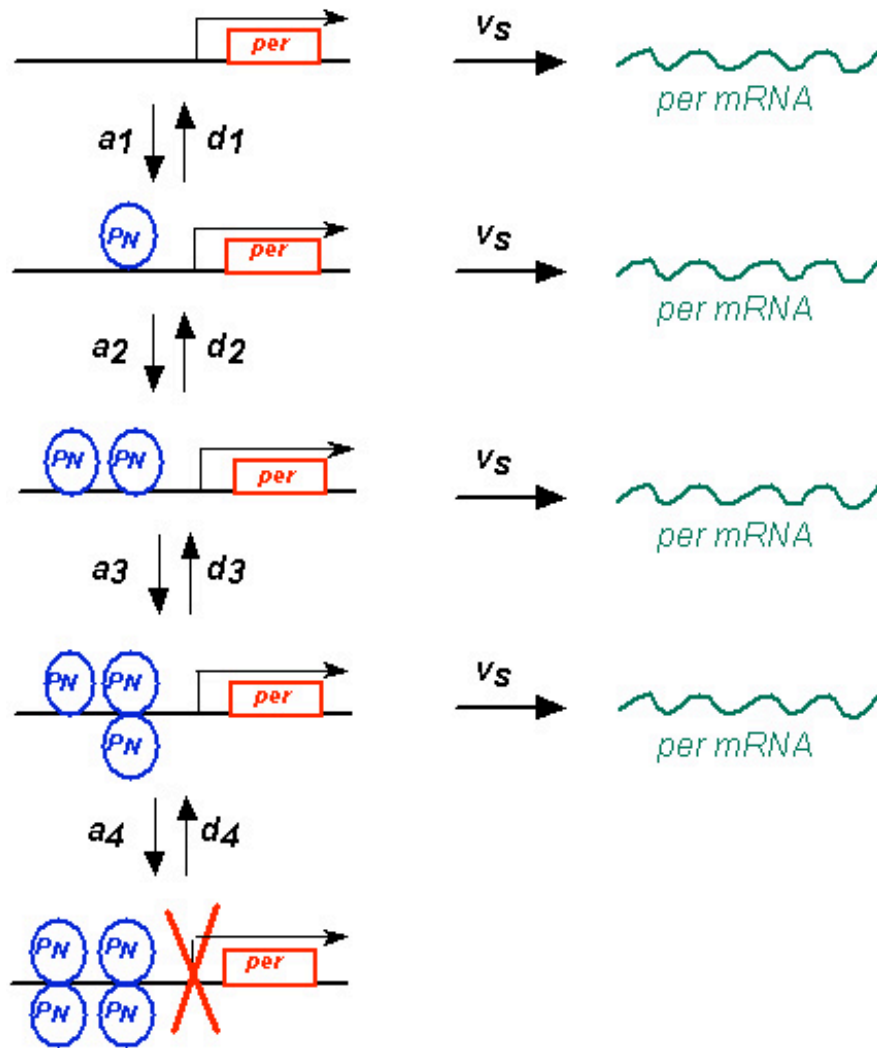
$$\frac{dP_0}{dt} = k_s M_P - v_1 \frac{P_0}{K_1 + P_0} + v_2 \frac{P_1}{K_2 + P_1}$$

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

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

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

Cooperative protein-DNA binding



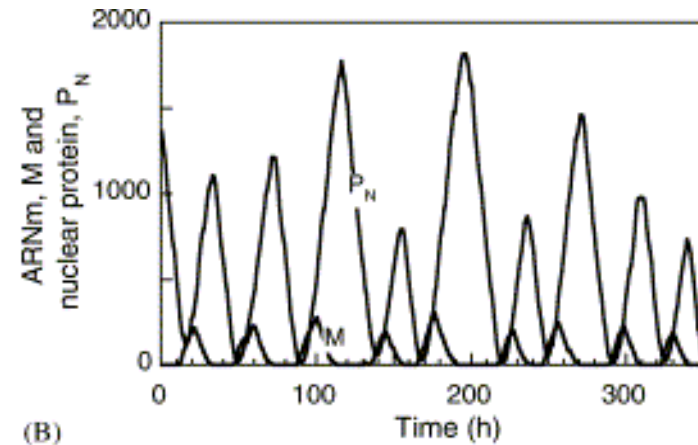
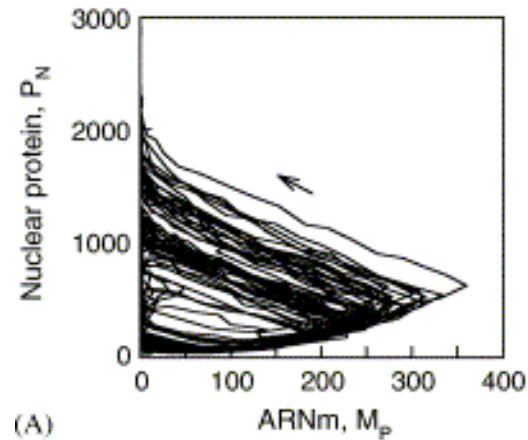
We define γ :

$$a_i \rightarrow a_i / \gamma \quad (i = 1, \dots, 4)$$

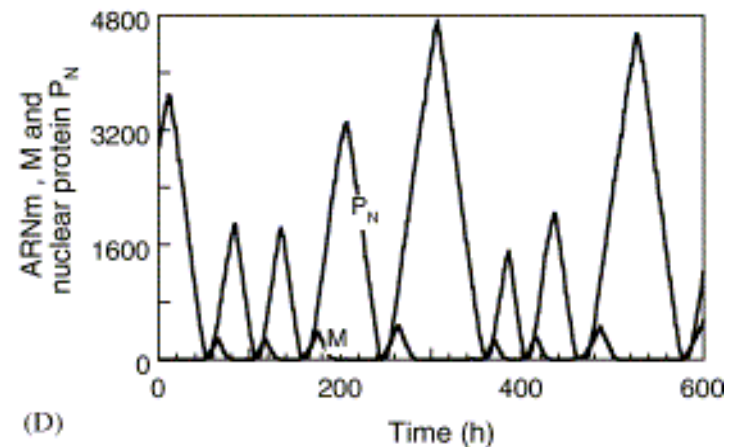
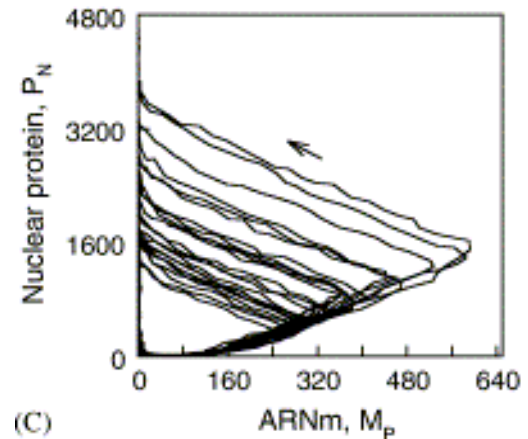
$$d_i \rightarrow d_i / \gamma \quad (i = 1, \dots, 4)$$

Influence of the protein-DNA binding rate

$\gamma = 100$



$\gamma = 1000$



Gonze D, Halloy J, Goldbeter A (2004) Emergence of coherent oscillations in stochastic models for circadian rhythms. *Physica A* 342: 221-233.

Developed deterministic model

$$\frac{dG}{dt} = -a_1 GP_N + d_1 [GP_N],$$

$$\frac{d[GP_N]}{dt} = a_1 GP_N - d_1 [GP_N] - a_2 [GP_N] P_N + d_2 [GP_{N2}],$$

$$\frac{d[GP_{N2}]}{dt} = a_2 [GP_{N1}] P_N - d_2 [GP_{N2}] - a_3 [GP_{N2}] P_N + d_3 [GP_{N3}],$$

$$\frac{d[GP_{N3}]}{dt} = a_3 [GP_{N2}] P_N - d_3 [GP_{N3}] - a_4 [GP_{N3}] P_N + d_4 [GP_{N4}],$$

$$\frac{d[GP_{N4}]}{dt} = a_4 [GP_{N3}] P_N - d_4 [GP_{N4}],$$

$$\frac{dM}{dt} = v_s (G + [GP_N] + [GP_{N2}] + [GP_{N3}]) - k_{11} ME_m + k_{12} C_m,$$

$$\frac{dE_m}{dt} = -k_{m1} ME_m + k_{m2} C_m + k_{m3} C_m,$$

$$\frac{dC_m}{dt} = k_{m1} ME_m - k_{m2} C_m - k_{m3} C_m,$$

$$\frac{dP_0}{dt} = k_5 M - k_{11} P_0 E_1 + k_{12} C_1 + k_{23} C_2,$$

$$\frac{dE_1}{dt} = -k_{11} P_0 E_1 + k_{12} C_1 + k_{13} C_1,$$

$$\frac{dC_1}{dt} = k_{11} P_0 E_1 - k_{12} C_1 - k_{13} C_1,$$

$$\frac{dP_1}{dt} = -k_{21} P_1 E_2 + k_{22} C_2 + k_{13} C_1 - k_{31} P_1 E_3 + k_{32} C_3 + k_{43} C_4,$$

$$\frac{dE_2}{dt} = -k_{21} P_1 E_2 + k_{22} C_2 + k_{23} C_2,$$

$$\frac{dC_2}{dt} = k_{21} P_1 E_2 - k_{22} C_2 - k_{23} C_2,$$

$$\frac{dP_2}{dt} = k_{33} C_3 - k_{41} P_2 E_4 + k_{42} C_4 - k_{d1} P_2 E_d + k_{d2} C_d - k_1 P_2 + k_2 P_N,$$

$$\frac{dE_3}{dt} = -k_{31} P_1 E_3 + k_{32} C_3 + k_{33} C_3,$$

$$\frac{dC_3}{dt} = k_{31} P_1 E_3 - k_{32} C_3 - k_{33} C_3,$$

$$\frac{dE_4}{dt} = -k_{41} P_2 E_4 + k_{42} C_4 + k_{43} C_4,$$

$$\frac{dC_4}{dt} = k_{41} P_2 E_4 - k_{42} C_4 - k_{43} C_4,$$

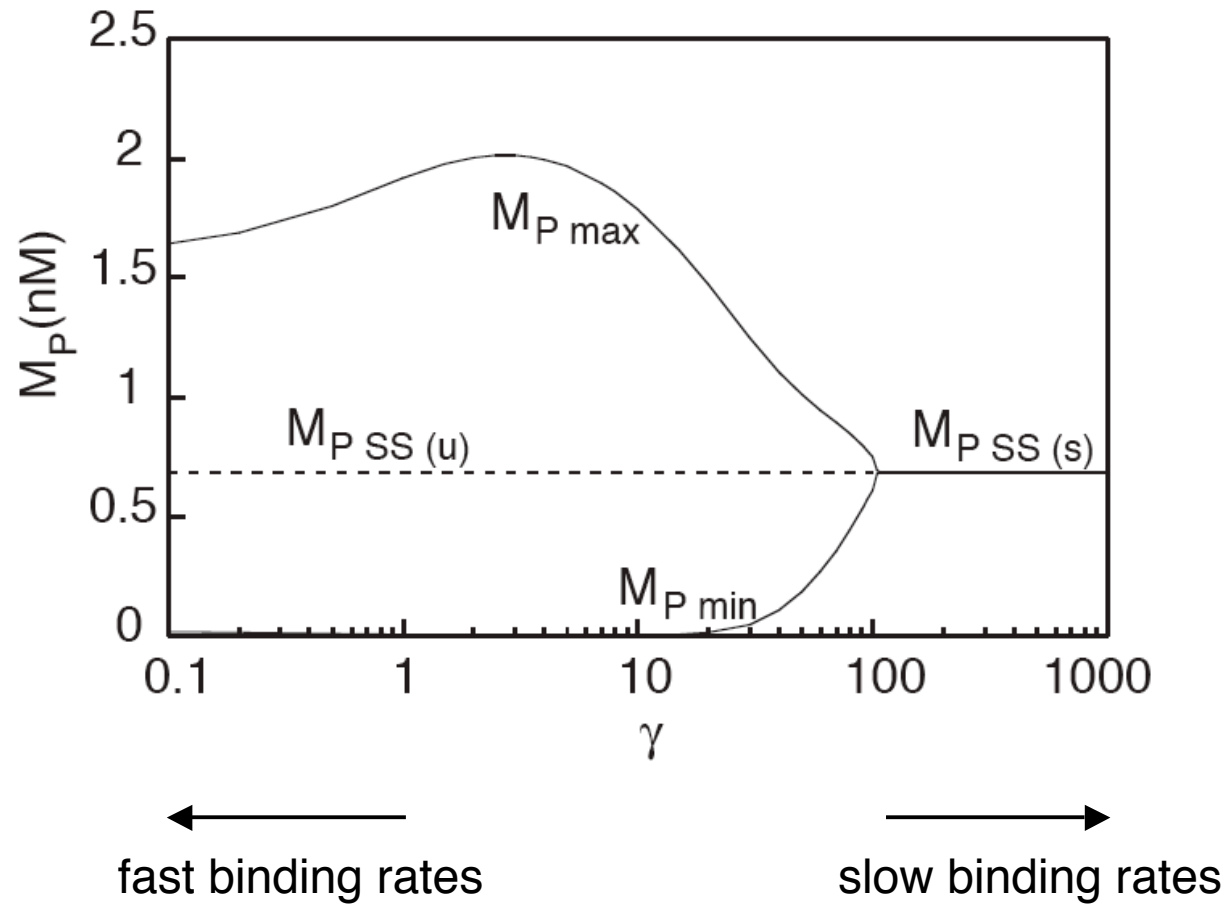
$$\frac{dE_d}{dt} = -k_{d1} P_2 E_d + k_{d2} C_d + k_{d3} C_d,$$

$$\frac{dC_d}{dt} = k_{d1} P_2 E_d - k_{d2} C_d - k_{d3} C_d,$$

$$\begin{aligned} \frac{dP_N}{dt} = & -a_1 GP_N + d_1 [GP_N] - a_2 [GP_{N1}] P_N + d_2 [GP_{N2}] - a_3 [GP_{N2}] P_N \\ & + d_3 [GP_{N3}] - a_4 [GP_{N3}] P_N + d_4 [GP_{N4}] + k_1 P_2 - k_2 P_N \end{aligned}$$

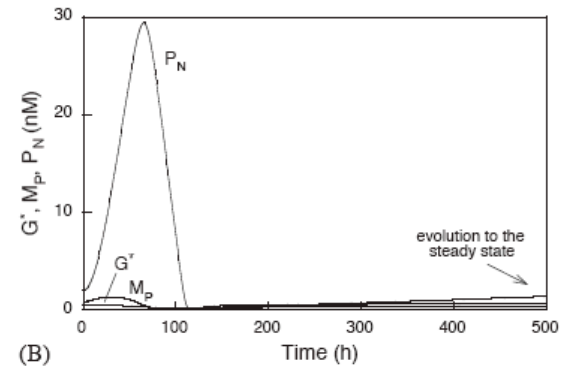
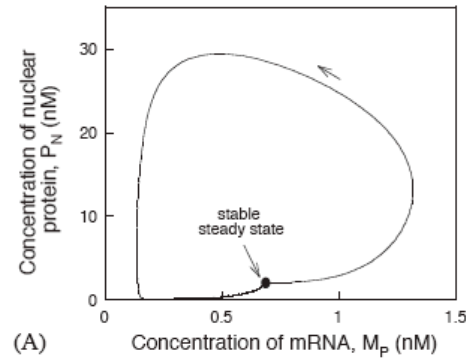
with $G_{tot} = G + GP_N + GP_{N2} + GP_{N3} + GP_{N4} = 1$.

Deterministic model: bifurcation diagram

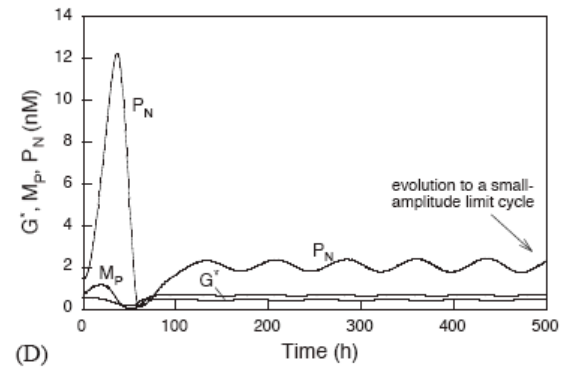
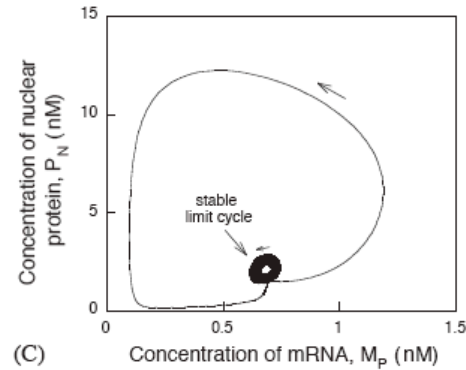


Developed deterministic model: excitability

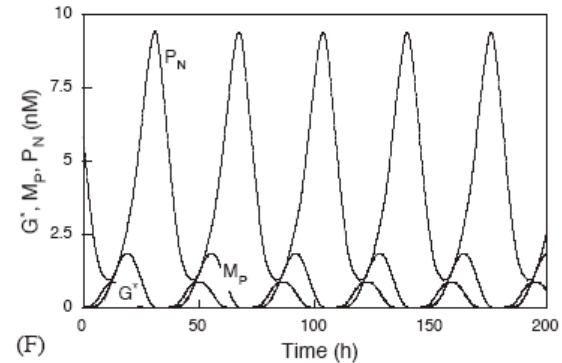
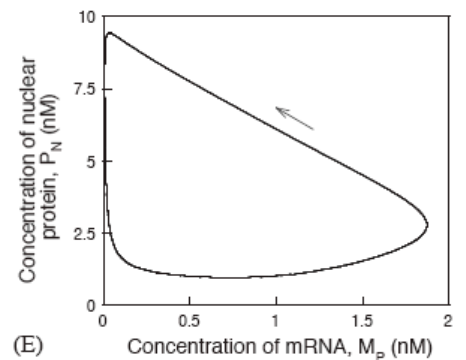
$\gamma = 1000$



$\gamma = 100$



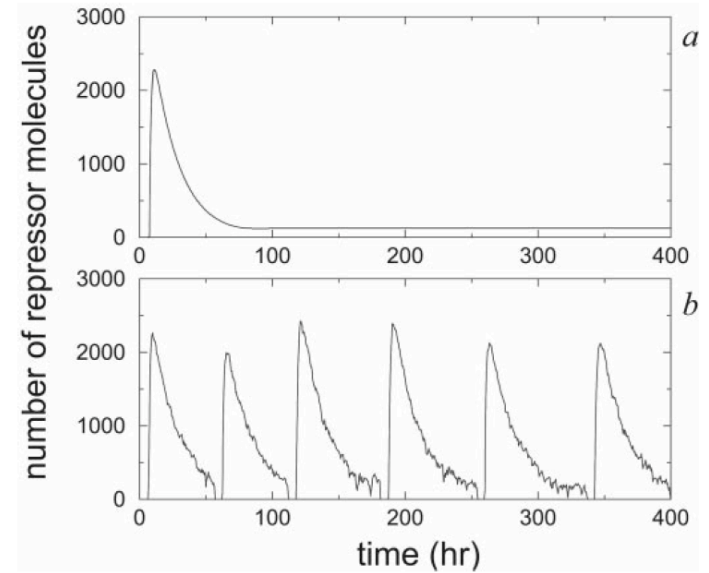
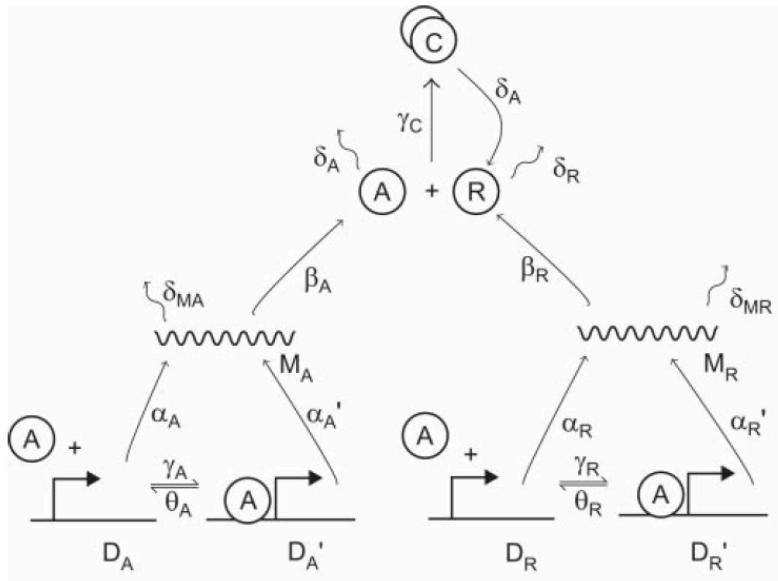
$\gamma = 1$



Mechanisms of noise-resistance

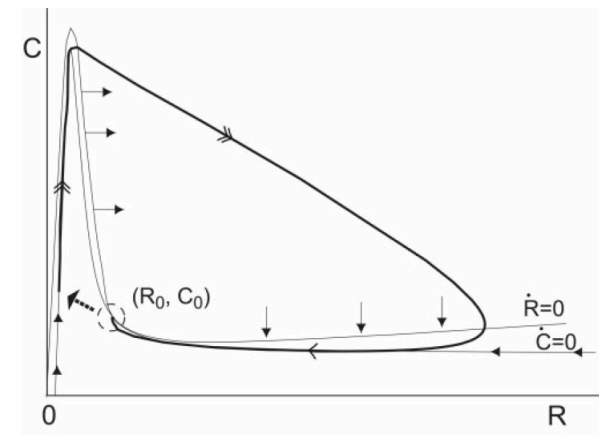
Mechanisms of noise-resistance in genetic oscillators

Vilar, Kueh, Barkai, Leibler, *PNAS* (2002) 99: 5988-5992



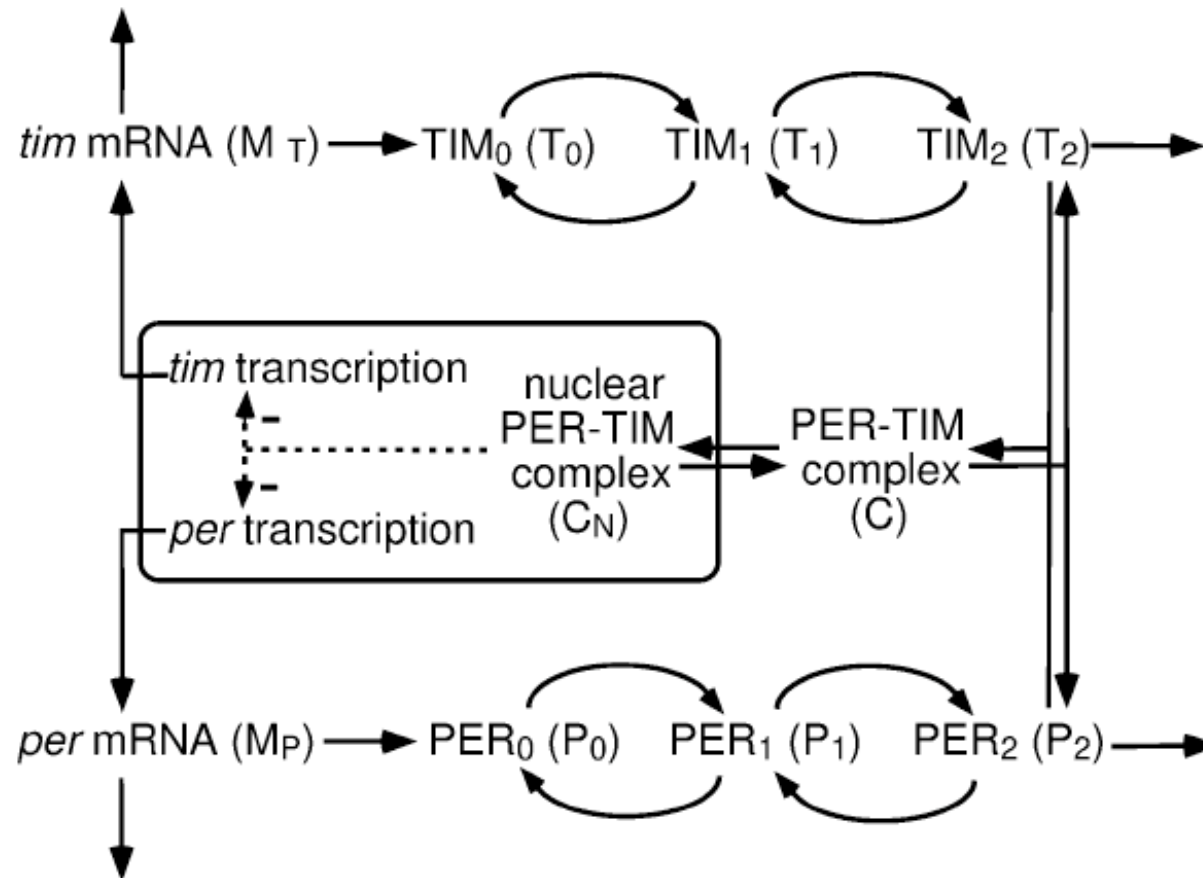
$$\frac{dR}{dt} = \frac{\beta_R}{\delta_{M_R}} \frac{\alpha_R \theta_R + \alpha'_R \gamma_R \tilde{A}(R)}{\theta_R + \gamma_R \tilde{A}(R)} - \gamma_C \tilde{A}(R) R + \delta_A C - \delta_R R$$

$$\frac{dC}{dt} = \gamma_C \tilde{A}(R) R - \delta_A C$$



Effect of noise in more complex models

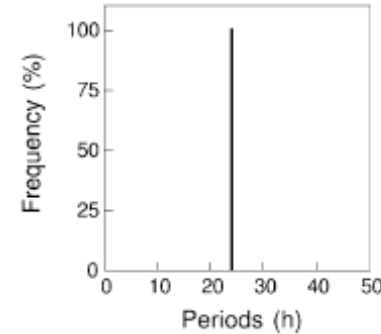
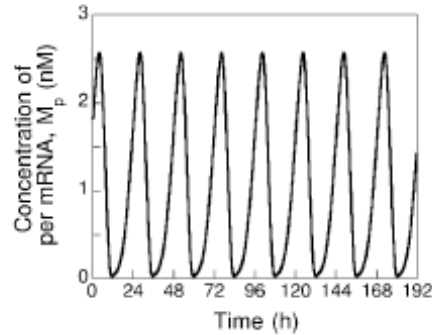
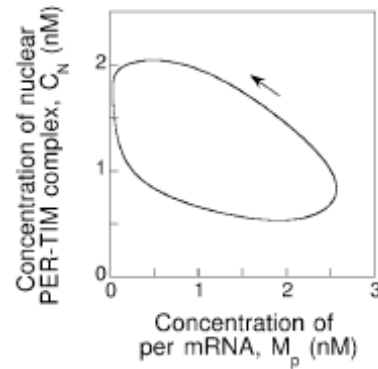
PER-TIM model for the *Drosophila* circadian clock



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

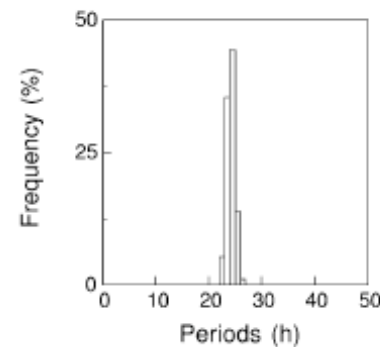
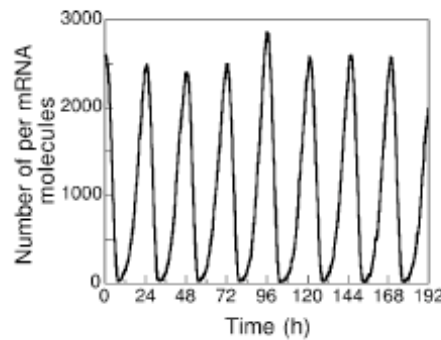
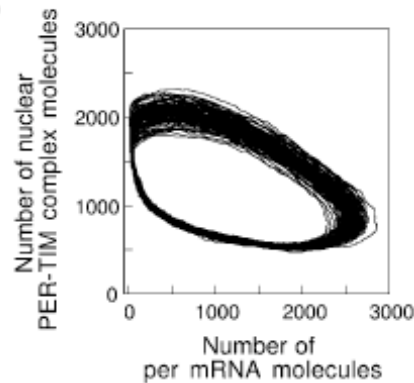
Effect of noise in more complex models

A



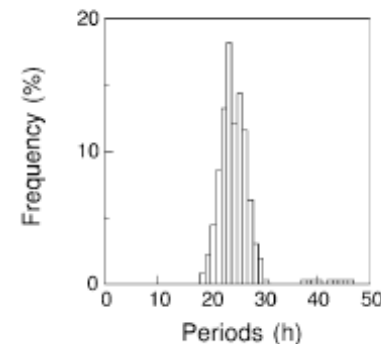
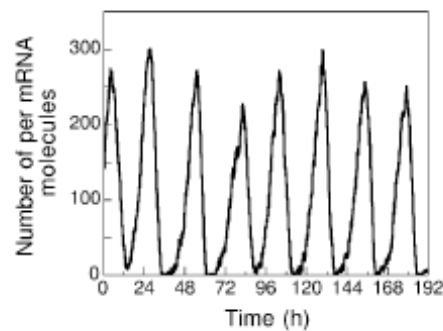
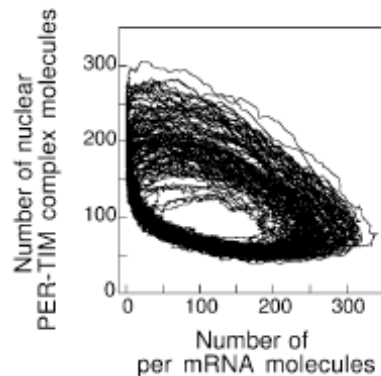
**Deterministic limit
cycle oscillations**

B



**Stochastic limit
cycle oscillations
($\Omega = 1000$)**

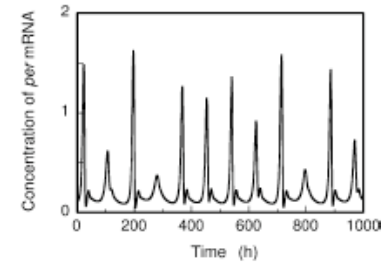
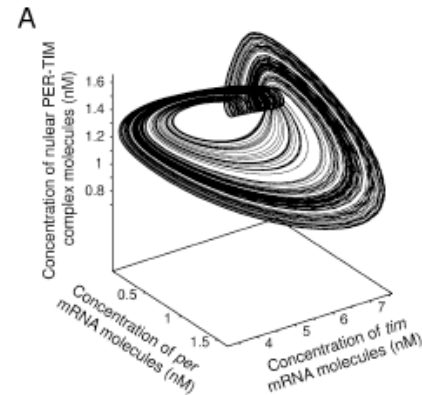
C



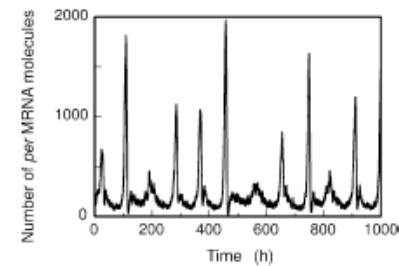
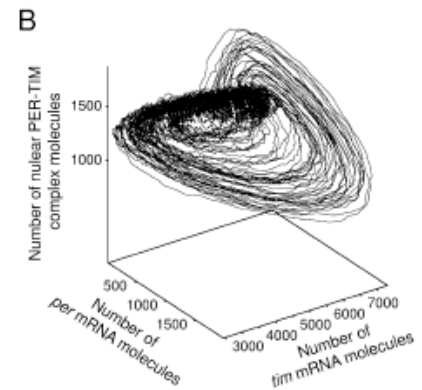
**Stochastic limit
cycle oscillations
($\Omega = 100$)**

Effect of noise in more complex models

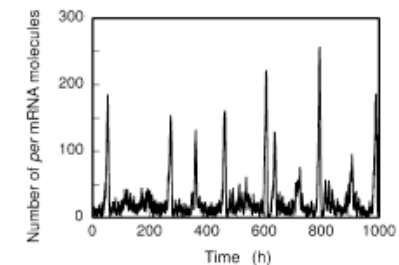
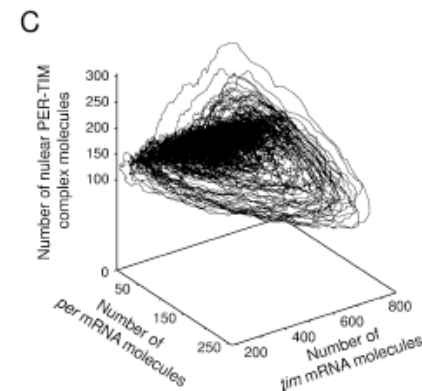
Effect of noise on the chaotic behavior



**Deterministic
chaotic behavior**



**Stochastic chaotic
behavior
($\Omega = 1000$)**

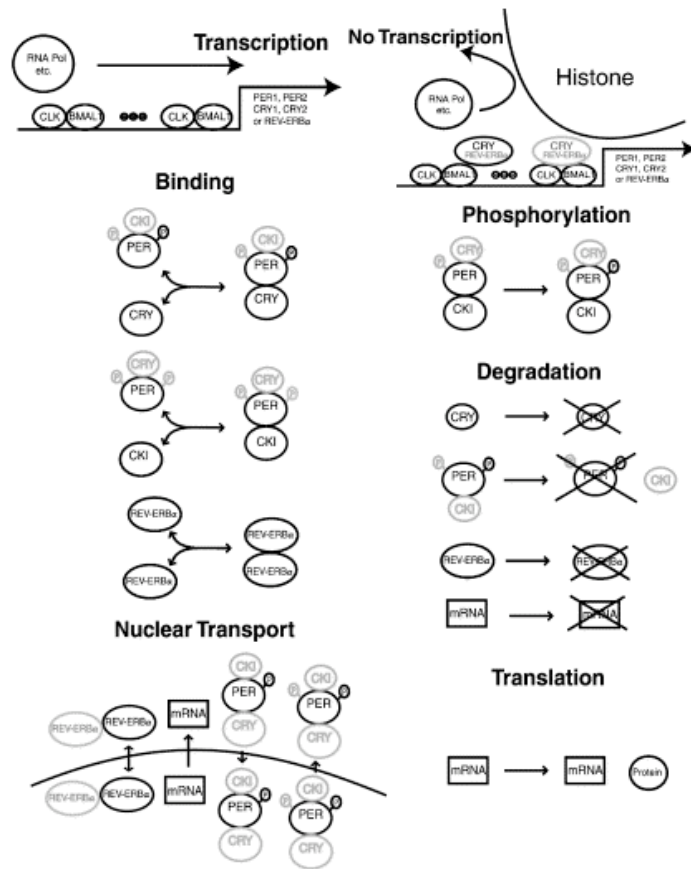


**Stochastic chaotic
behavior
($\Omega = 100$)**

Mutation and robustness to noise

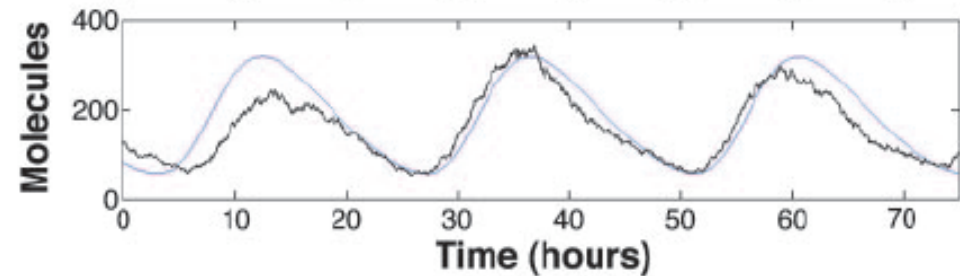
Stochastic simulation of the mammalian circadian clock

Forger and Peskin, *PNAS* (2005) 102: 321-324

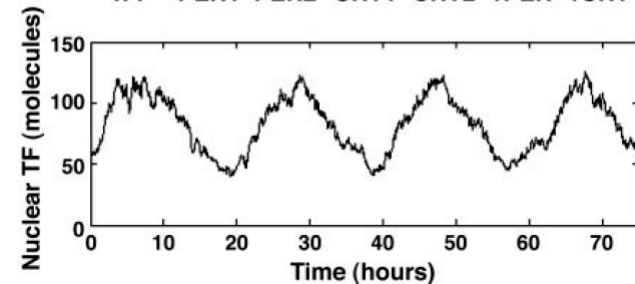
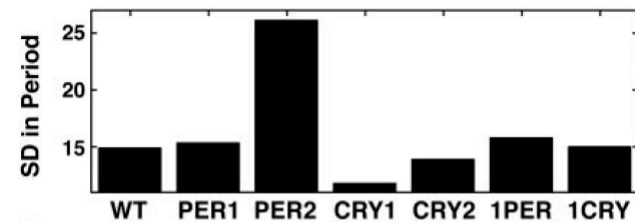


Model for the mammalian circadian clock
(74 variables!)

Higher robustness if the binding rate is high



Differential effect of the mutations on the robustness

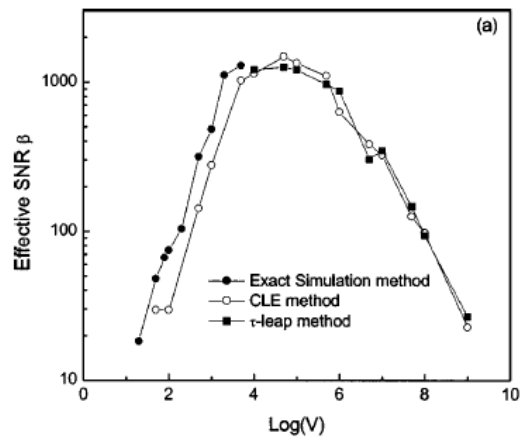
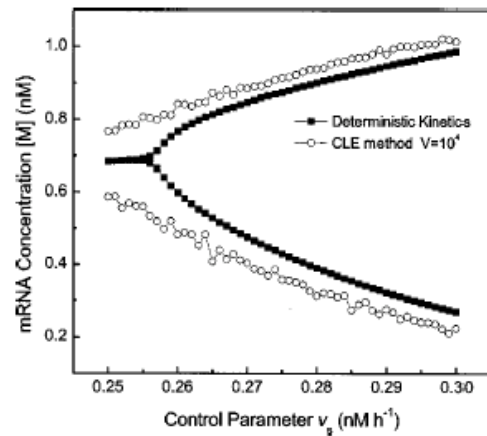


PER2 mutant

Stochastic resonance in circadian clock?

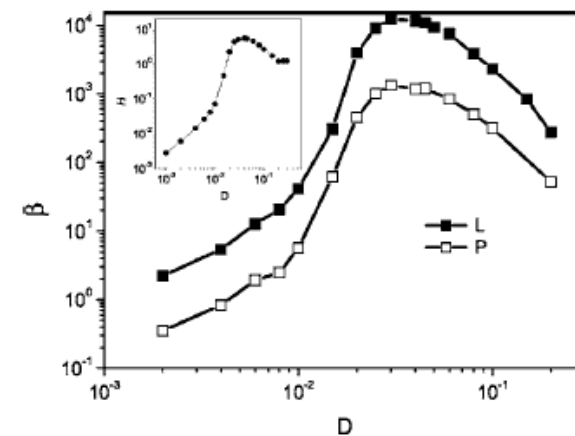
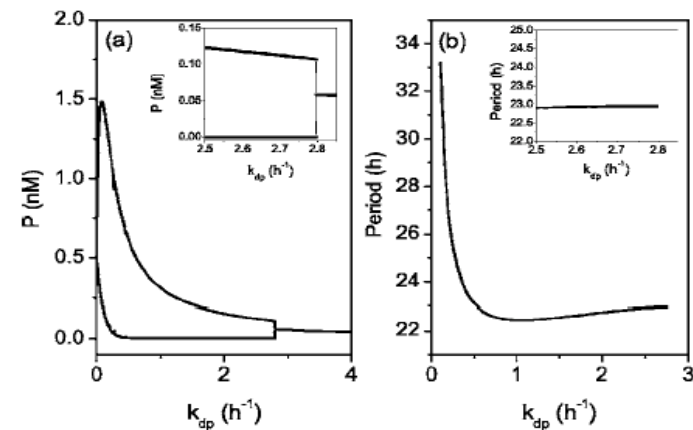
Internal noise stochastic resonance in a circadian clock system

Hou & Xin, *J Chem Phys* (2003) 119: 11508



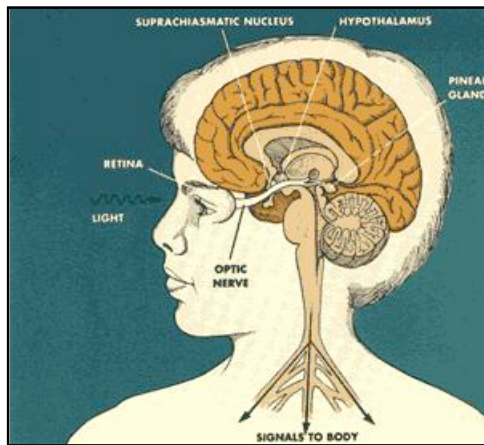
Light-noise induced supra-threshold circadian oscillations and coherent resonance in *Drosophila*

Yi & Jia, *Phys Rev E* (2005) 72: 012902



Coupling circadian oscillators

Mammals: SCN

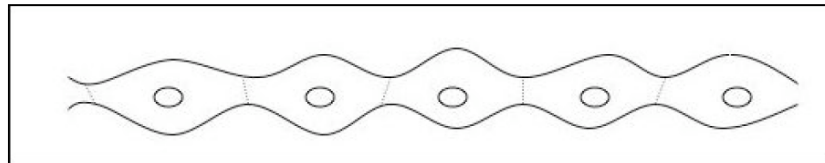
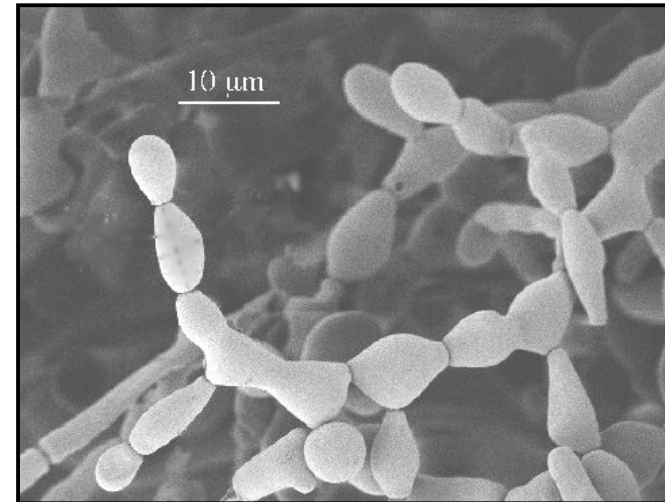
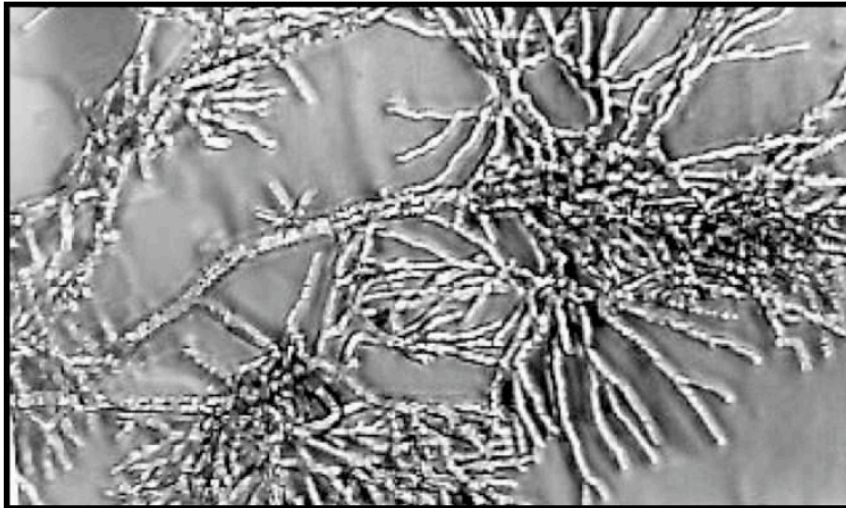


Neurospora crassa



Coupling circadian oscillators: *Neurospora*

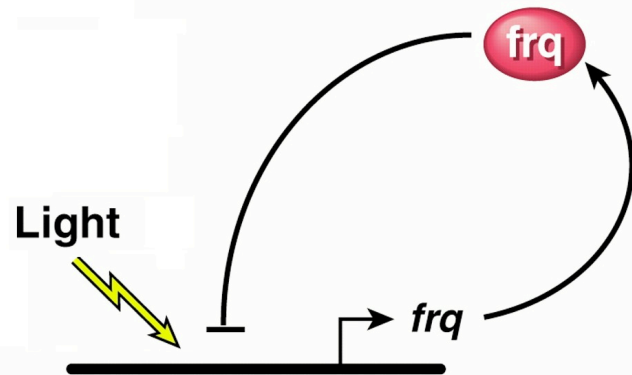
Neurospora crassa



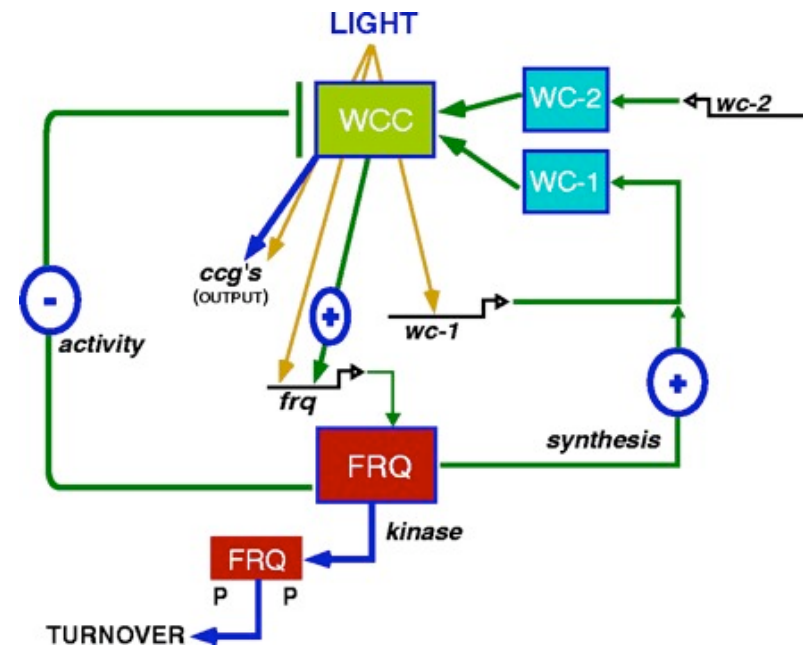
syncytium

Neurospora: molecular mechanism

Neurospora crassa: Molecular mechanism of the circadian clock

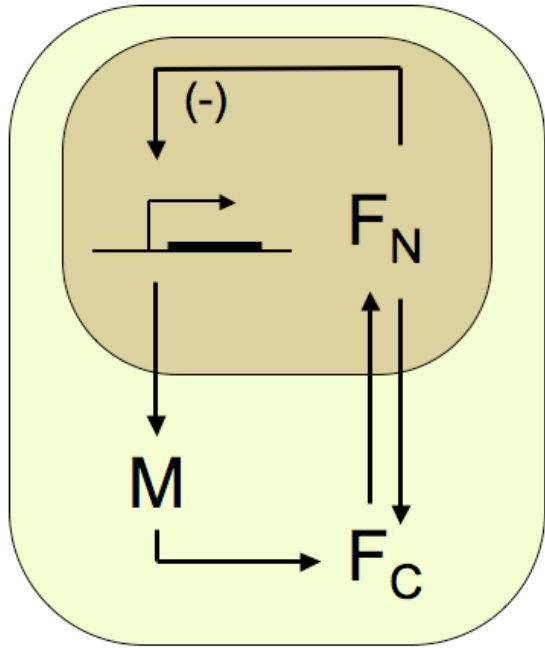


Aronson BD, Johnson KA, Loros JJ, Dunlap LC (1994) Negative feedback defining a circadian clock: autoregulation of the clock gene frequency. *Science*. 263: 1578-84.

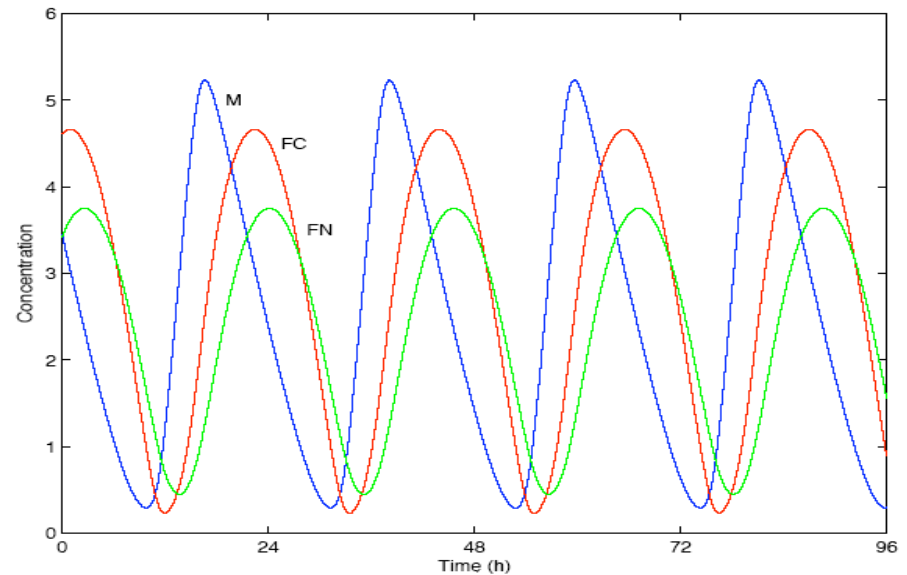


Lee K, Loros JJ, Dunlap JC (2000) Interconnected feedback loops in the *Neurospora* circadian system. *Science*. 289: 107-10.

Neurospora circadian clock: single-cell model

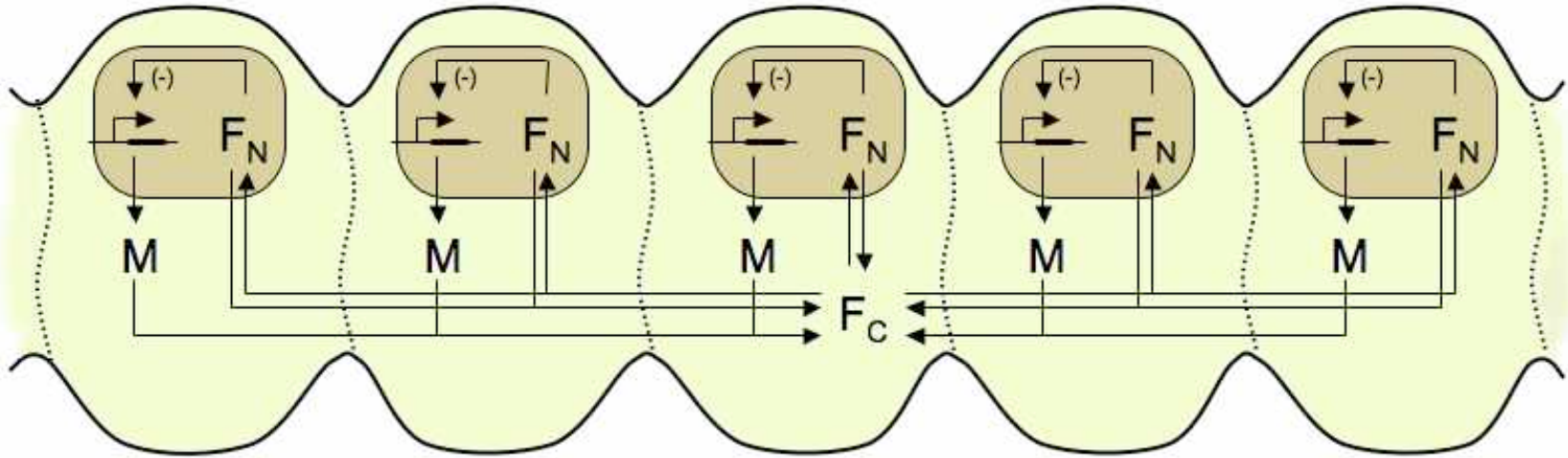


$$\begin{aligned} \frac{dM}{dt} &= \lambda v_s \frac{K_I^n}{K_I^n + F_N^n} - v_m \frac{M}{K_m + M} \\ \frac{dF_c}{dt} &= k_s M - v_d \frac{F_c}{K_d + F_c} - k_1 F_c + k_2 F_n \\ \frac{dF_n}{dt} &= k_1 F_c - k_2 F_n \end{aligned}$$

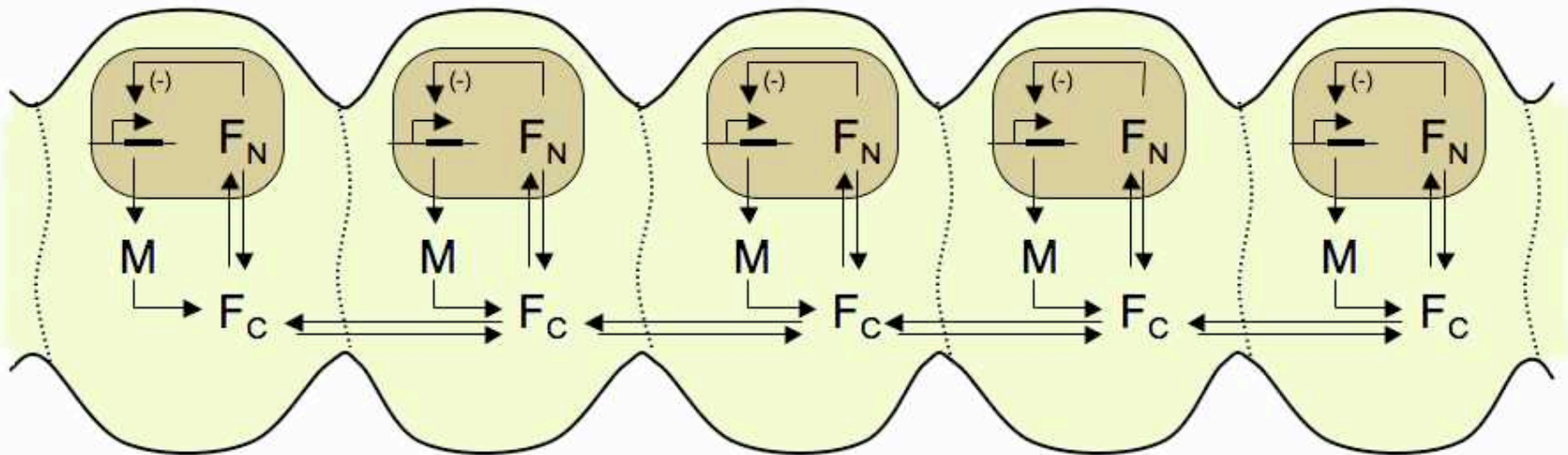


Neurospora circadian clock: coupled model

Global coupling



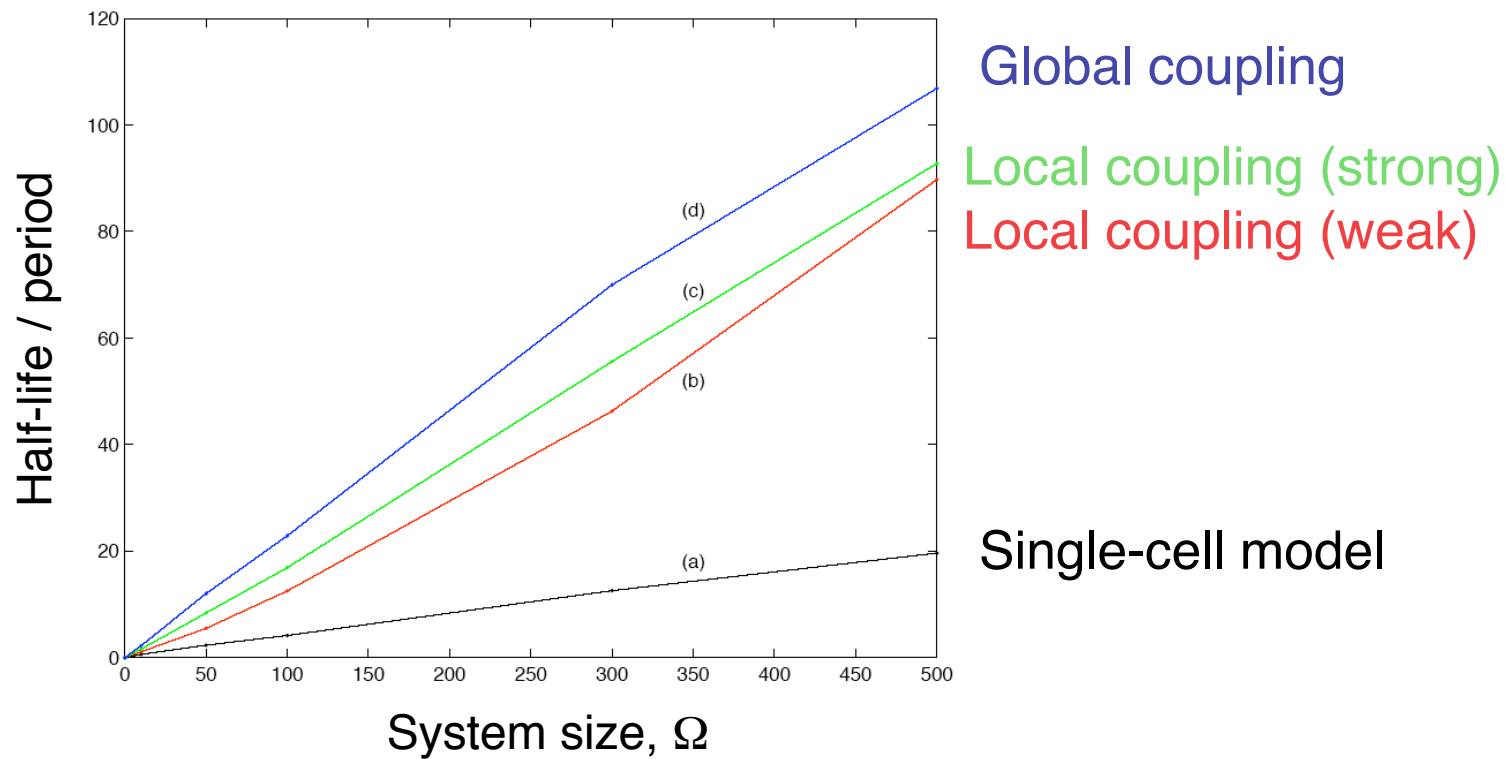
Local coupling



Robustness of the coupled model

Robustness of the coupled model for the *Neurospora* circadian clock

Half-life of the auto-correlation function



Conclusions

- **Robust circadian oscillations** are observed for a limited number of molecules, i.e. some tens mRNA molecules and hundreds proteins molecules.
- **Cooperativity** increases the robustness of the oscillations.
- The **periodic forcing** of the oscillations (LD cycle) increases the robustness by stabilizing the phase of the oscillations.
- The proximity of a **bifurcation point** decreases the robustness of the oscillations. In particular, near an excitable steady state, highly irregular oscillations are observed.
- **Coupling** between cells increases the robustness of the oscillations.