Cinvestav-Monterrey

Modelo mínimo del Ciclo circadiano en mamíferos

Leonardo López Ortiz

Ritmo circadiano

Evento fisiológico que ocurre con una frecuencia de alrededor de 24 horas.

(Circa, “Aproximadamente”, dies, “dia”)

Propiedades principales:

- Endógeno (oscilaciones autosostenidas)
- Se mantiene en un rango de temperaturas fisiológicas
- Sincronizable con señales periódicas externas (luz solar principalmente)

Reloj circadiano primario

Ubicado en el núcleo supraquiasmatico con cerca de 8000 neuronas identificadas (hipotálamo), y con conexión directa a la retina.

Regulación de :

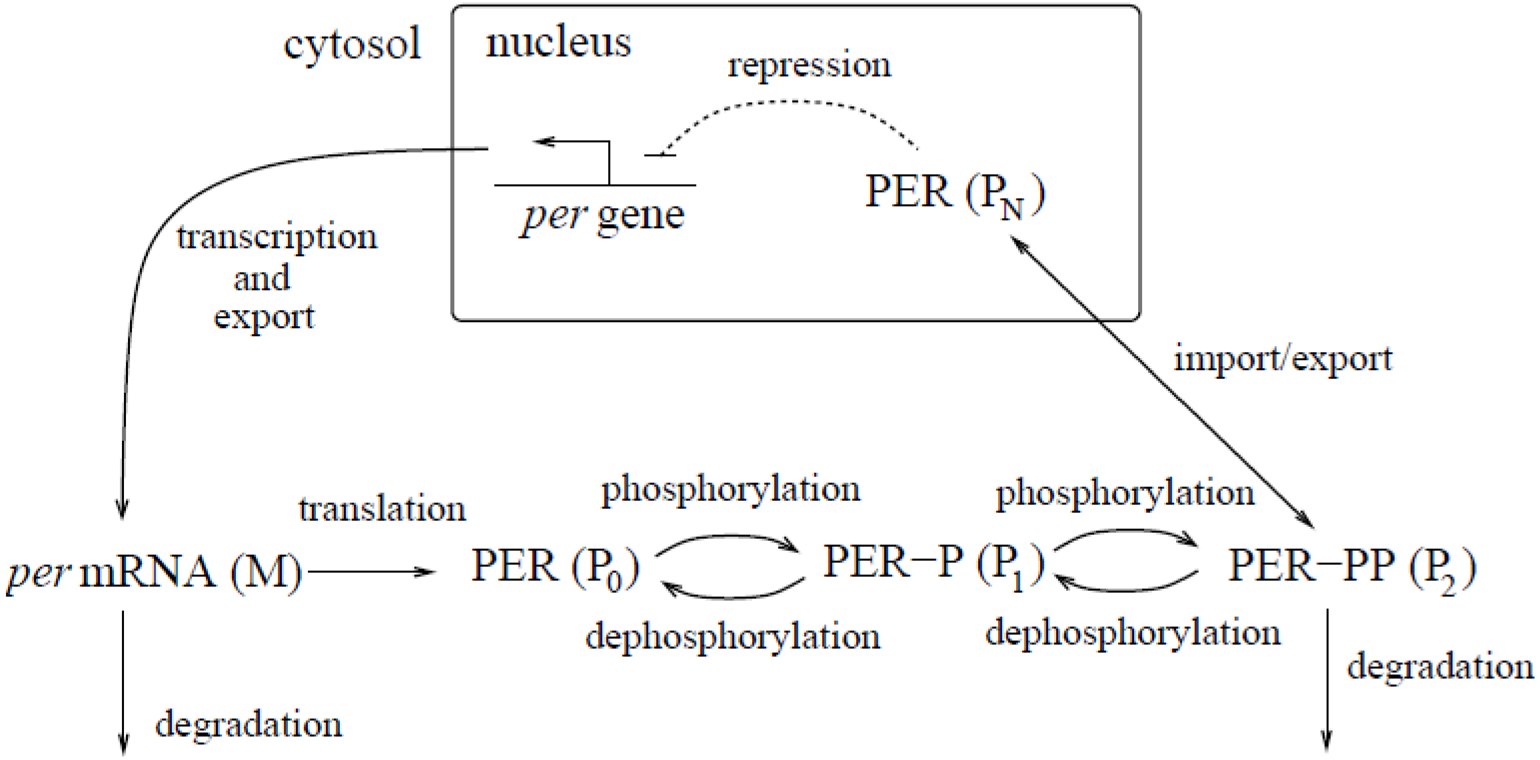
- Sueño – vigilia
- Temperatura corporal
- Presión arterial
- Hormonas
- Respuesta inmune

Si es perturbado:

- Desorden del sueño
- Jet lag
- Depresión
- Estrés
- Cáncer

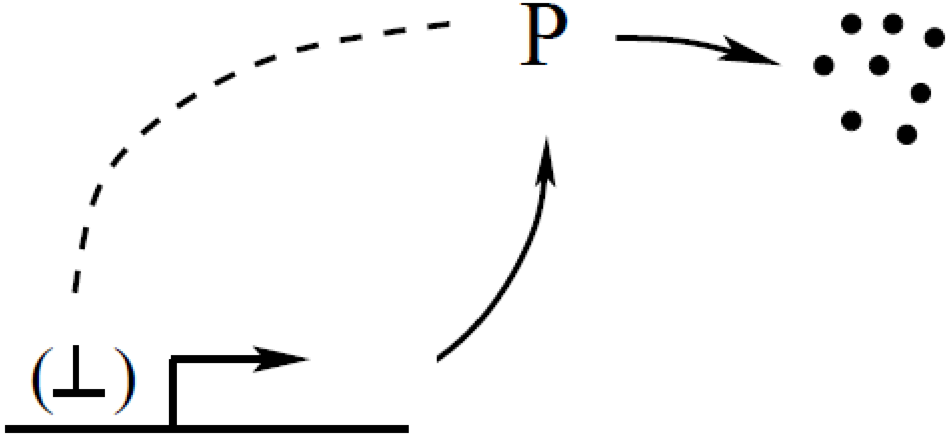
Bases moleculares

Drosophila M.

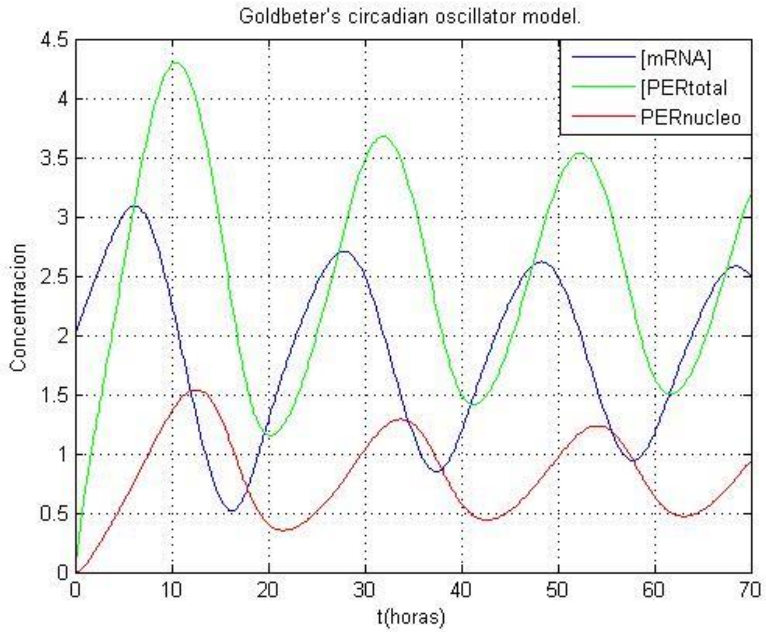


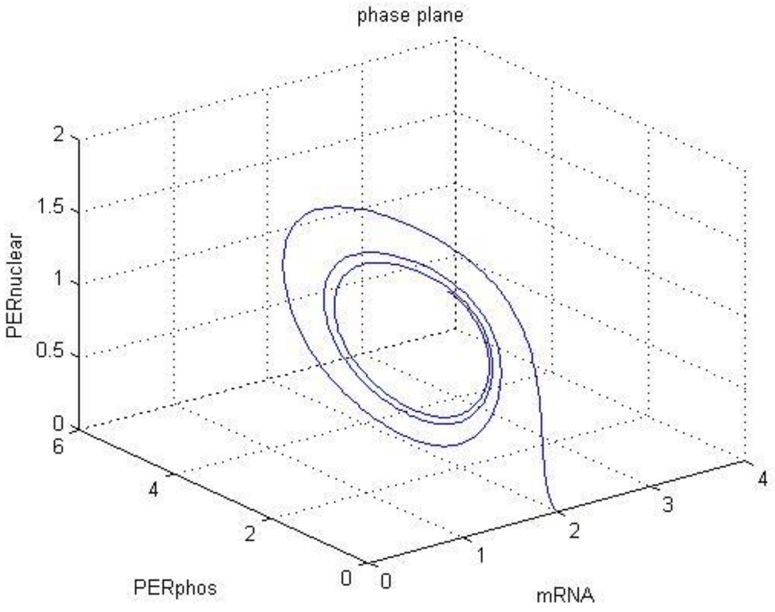
Goldbeter, A. (1996). Biochemical Oscillations and Cellular Rhythms: The Molecular Bases of Periodic and Chaotic Behaviour, Cambridge, UK: Cambridge University Press.

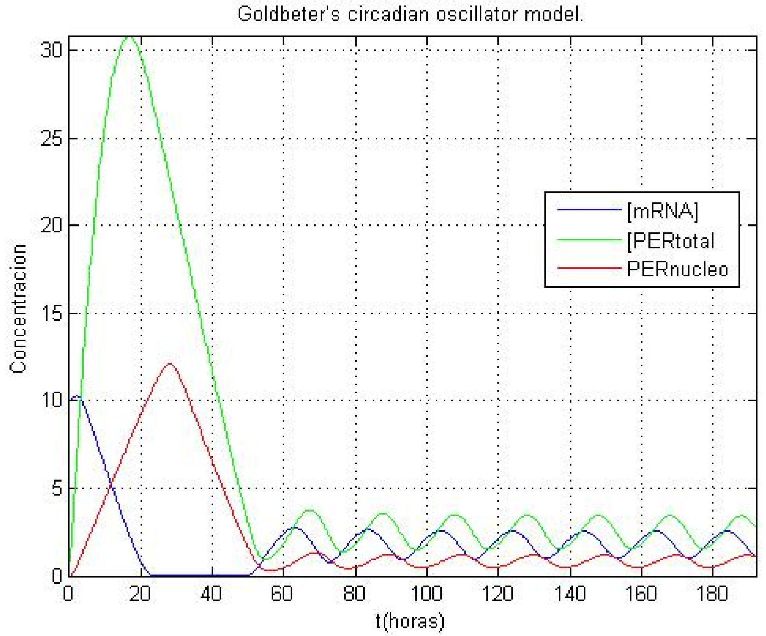
Realimentación negativa (auto inhibición)



$$
\begin{aligned}
\frac{d}{dt}m(t) &= \frac{v_s}{1+(p_N(t)/K_I)^n} - \frac{v_m m(t)}{K_{m1}+m(t)} \\
\frac{d}{dt}p_0(t) &= k_s m(t) - \frac{V_1 p_0(t)}{K_1+p_0(t)} + \frac{V_2 p_1(t)}{K_2+p_1(t)} \\
\frac{d}{dt}p_1(t) &= \frac{V_1 p_0(t)}{K_1+p_0(t)} - \frac{V_2 p_1(t)}{K_2+p_1(t)} - \frac{V_3 p_1(t)}{K_3+p_1(t)} + \frac{V_4 p_2(t)}{K_4+p_2(t)} \\
\frac{d}{dt}p_2(t) &= \frac{V_3 p_1(t)}{K_3+p_1(t)} - \frac{V_4 p_2(t)}{K_4+p_2(t)} - k_1 p_2(t) + k_2 p_N(t) - \frac{v_d p_2(t)}{K_d+p_2(t)} \\
\frac{d}{dt}p_N(t) &= k_1 p_2(t) - k_2 p_N(t).
\end{aligned}
$$


Goldbeter's circadian oscillator model.
[mRNA]
[PERtotal
PERnucleo
Concentracion
t(horas)


phase plane
PERnuclear
PERphos
mRNA


Goldbeter's circadian oscillator model.
[mRNA]
[PERtotal
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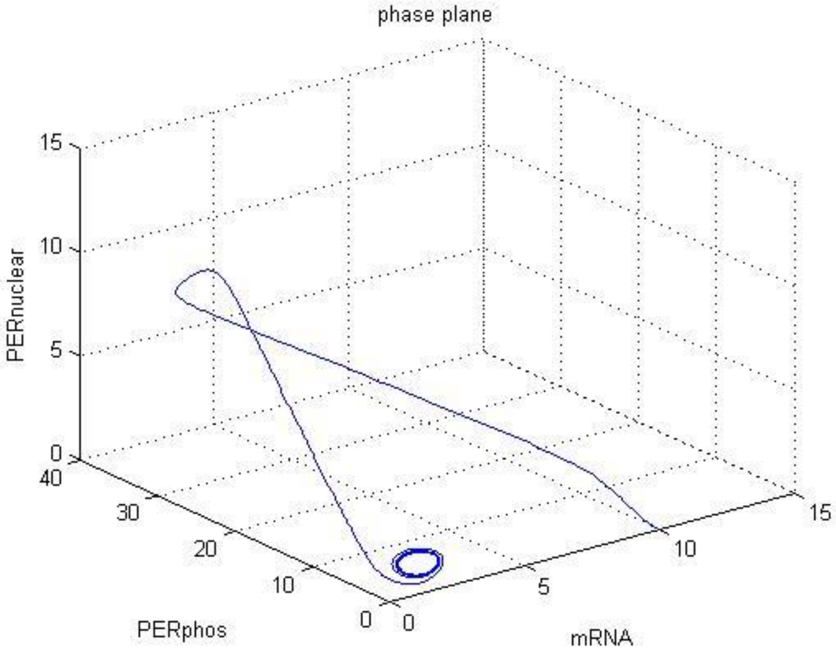
Concentracion
t(horas)

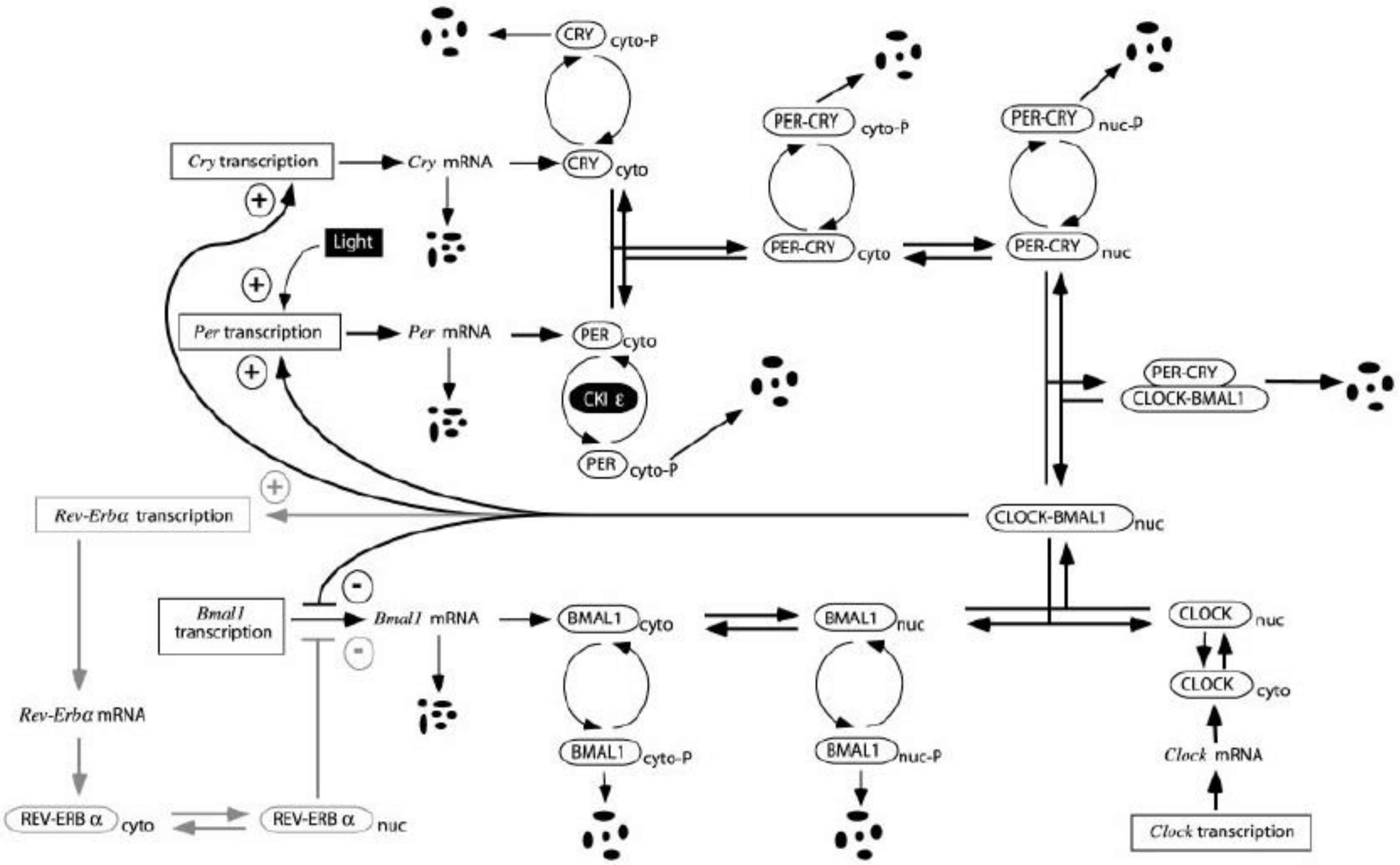

phase plane
PERnuclear
PERphos
mRNA

Toward a detailed computational model for the mammalian circadian clock

Jean-Christophe Leloup* 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, April 10, 2003 (received for review November 25, 2002)



mRNA’s de Periodo, cryptocromo y Bmal1

$$\frac{\mathrm{d}M_{\mathrm{P}}}{\mathrm{d}t} = v_{\mathrm{sP}}\frac{B_{\mathrm{N}}^{\mathrm{n}}}{K_{\mathrm{AP}}^{\mathrm{n}} + B_{\mathrm{N}}^{\mathrm{n}}} - v_{\mathrm{mP}}\frac{M_{\mathrm{P}}}{K_{\mathrm{mP}} + M_{\mathrm{P}}} - k_{\mathrm{dmp}}M_{\mathrm{P}} \quad \textbf{[1]}$$

$$\frac{\mathrm{d}M_{\mathrm{C}}}{\mathrm{d}t} = v_{\mathrm{sC}}\frac{B_{\mathrm{N}}^{\mathrm{n}}}{K_{\mathrm{AC}}^{\mathrm{n}} + B_{\mathrm{N}}^{\mathrm{n}}} - v_{\mathrm{mC}}\frac{M_{\mathrm{C}}}{K_{\mathrm{mC}} + M_{\mathrm{C}}} - k_{\mathrm{dmc}}M_{\mathrm{C}} \quad \textbf{[2]}$$

$$\frac{\mathrm{d}M_{\mathrm{B}}}{\mathrm{d}t} = v_{\mathrm{sB}}\frac{K_{\mathrm{IB}}^{\mathrm{m}}}{K_{\mathrm{IB}}^{\mathrm{m}} + B_{\mathrm{N}}^{\mathrm{m}}} - v_{\mathrm{mB}}\frac{M_{\mathrm{B}}}{K_{\mathrm{mB}} + M_{\mathrm{B}}} - k_{\mathrm{dmb}}M_{\mathrm{B}} \quad \textbf{[3]}$$

$$\frac{\mathrm{d}P_{\mathrm{C}}}{\mathrm{d}t} = k_{\mathrm{sP}}M_{\mathrm{P}} - V_{1\mathrm{P}}\frac{P_{\mathrm{C}}}{K_{\mathrm{p}} + P_{\mathrm{C}}} + V_{2\mathrm{P}}\frac{P_{\mathrm{CP}}}{K_{\mathrm{dp}} + P_{\mathrm{CP}}} + k_4 PC_C - k_3 P_C C_C - k_{\mathrm{dn}}P_{\mathrm{C}} \quad \textbf{[4]}$$

$$\frac{\mathrm{d}C_{\mathrm{C}}}{\mathrm{d}t} = k_{\mathrm{sC}}M_{\mathrm{C}} - V_{1\mathrm{C}}\frac{C_{\mathrm{C}}}{K_{\mathrm{p}} + C_{\mathrm{C}}} + V_{2\mathrm{C}}\frac{C_{\mathrm{CP}}}{K_{\mathrm{dp}} + C_{\mathrm{CP}}} + k_4 PC_C - k_3 P_C C_C - k_{\mathrm{dnc}}C_{\mathrm{C}} \quad \textbf{[5]}$$

Proteínas PER, CRY, BMAL1 en citosol fosforiladas y no fosforiladas

$$\frac{\mathrm{d}P_{\mathrm{CP}}}{\mathrm{d}t} = V_{1\mathrm{P}}\frac{P_{\mathrm{C}}}{K_{\mathrm{p}} + P_{\mathrm{C}}} - V_{2\mathrm{P}}\frac{P_{\mathrm{CP}}}{K_{\mathrm{dp}} + P_{\mathrm{CP}}} - v_{dPC}\frac{P_{\mathrm{CP}}}{K_{\mathrm{d}} + P_{\mathrm{CP}}} - k_{\mathrm{dn}}P_{\mathrm{CP}} \quad \textbf{[6]}$$

$$\frac{\mathrm{d}C_{\mathrm{CP}}}{\mathrm{d}t} = V_{1\mathrm{C}}\frac{C_{\mathrm{C}}}{K_{\mathrm{p}} + C_{\mathrm{C}}} - V_{2\mathrm{C}}\frac{C_{\mathrm{CP}}}{K_{\mathrm{dp}} + C_{\mathrm{CP}}} - v_{dCC}\frac{C_{\mathrm{CP}}}{K_{\mathrm{d}} + C_{\mathrm{CP}}} - k_{\mathrm{dn}}C_{\mathrm{CP}} \quad \textbf{[7]}$$

Complejo PER-CRY fosforilado y no fosforilado en citosol y en nucleo

$$\frac{\mathrm{d}PC_{\mathrm{C}}}{\mathrm{d}t} = -V_{1\mathrm{PC}}\frac{PC_{\mathrm{C}}}{K_{\mathrm{p}} + PC_{\mathrm{C}}} + V_{2\mathrm{PC}}\frac{PC_{\mathrm{CP}}}{K_{\mathrm{dp}} + PC_{\mathrm{CP}}} - k_4 PC_{\mathrm{C}} + k_3 P_{\mathrm{C}} C_{\mathrm{C}} + k_2 PC_{\mathrm{N}} - k_1 PC_{\mathrm{C}} - k_{\mathrm{dn}} PC_{\mathrm{C}} \quad \textbf{[8]}$$

$$\frac{\mathrm{d}PC_{\mathrm{N}}}{\mathrm{d}t} = -V_{3\mathrm{PC}}\frac{PC_{\mathrm{N}}}{K_{\mathrm{p}} + PC_{\mathrm{N}}} + V_{4\mathrm{PC}}\frac{PC_{\mathrm{NP}}}{K_{\mathrm{dp}} + PC_{\mathrm{NP}}} - k_2 PC_{\mathrm{N}} + k_1 PC_{\mathrm{C}} - k_7 B_{\mathrm{N}} PC_{\mathrm{N}} + k_8 I_{\mathrm{N}} - k_{\mathrm{dn}} PC_{\mathrm{N}} \quad \textbf{[9]}$$

$$\frac{\mathrm{d}PC_{\mathrm{CP}}}{\mathrm{d}t} = V_{1\mathrm{PC}}\frac{PC_{\mathrm{C}}}{K_{\mathrm{p}} + PC_{\mathrm{C}}} - V_{2\mathrm{PC}}\frac{PC_{\mathrm{CP}}}{K_{\mathrm{dp}} + PC_{\mathrm{CP}}} - v_{\mathrm{dPCC}}\frac{PC_{\mathrm{CP}}}{K_{\mathrm{d}} + PC_{\mathrm{CP}}} - k_{\mathrm{dn}} PC_{\mathrm{CP}} \quad \textbf{[10]}$$

$$\frac{\mathrm{d}PC_{\mathrm{NP}}}{\mathrm{d}t} = V_{3\mathrm{PC}}\frac{PC_{\mathrm{N}}}{K_{\mathrm{p}} + PC_{\mathrm{N}}} - V_{4\mathrm{PC}}\frac{PC_{\mathrm{NP}}}{K_{\mathrm{dp}} + PC_{\mathrm{NP}}} - v_{\mathrm{dPCN}}\frac{PC_{\mathrm{NP}}}{K_{\mathrm{d}} + PC_{\mathrm{NP}}} - k_{\mathrm{dn}} PC_{\mathrm{NP}} \quad \textbf{[11]}$$

Proteína BMAL1 fosforilada y no fosforilada en citosol y núcleo.
Complejo inactivo PER-CRY y BMAL-CLOCK en núcleo.

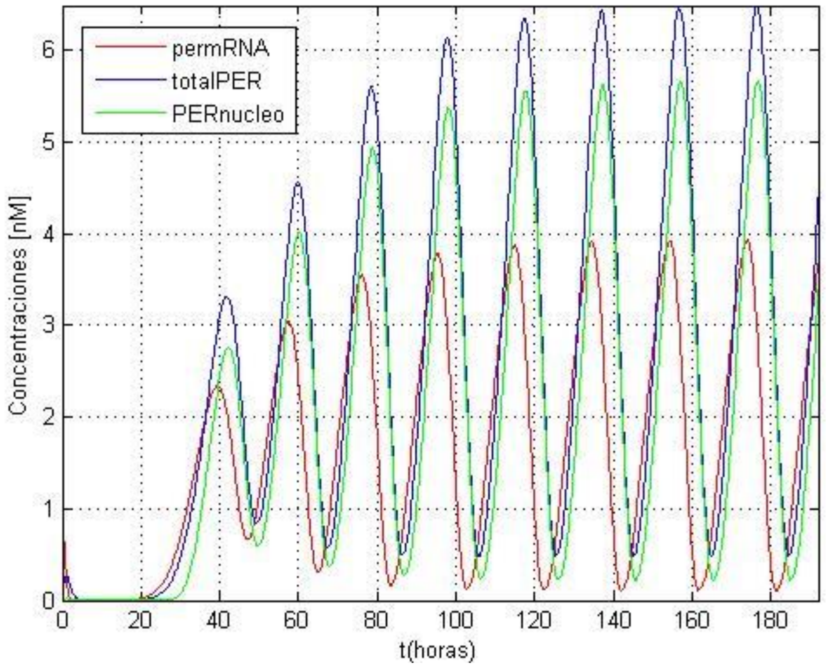
$$\frac{dB_C}{dt} = k_{sB}M_B - V_{1B}\frac{B_C}{K_p + B_C} + V_{2B}\frac{B_{CP}}{K_{dp} + B_{CP}} - k_5 B_C + k_6 B_N - k_{dn} B_C \qquad \textbf{[12]}$$

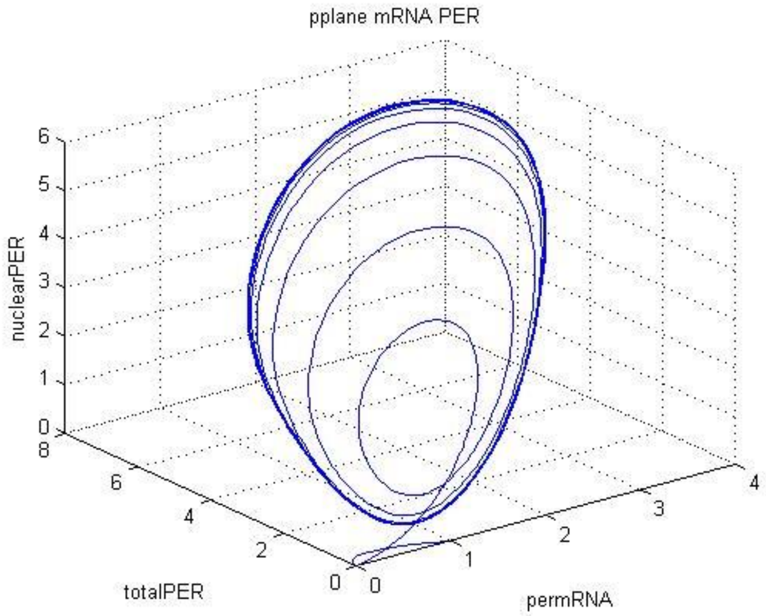
$$\frac{dB_{CP}}{dt} = V_{1B}\frac{B_C}{K_p + B_C} - V_{2B}\frac{B_{CP}}{K_{dp} + B_{CP}} - v_{dBC}\frac{B_{CP}}{K_d + B_{CP}} - k_{dn} B_{CP} \qquad \textbf{[13]}$$

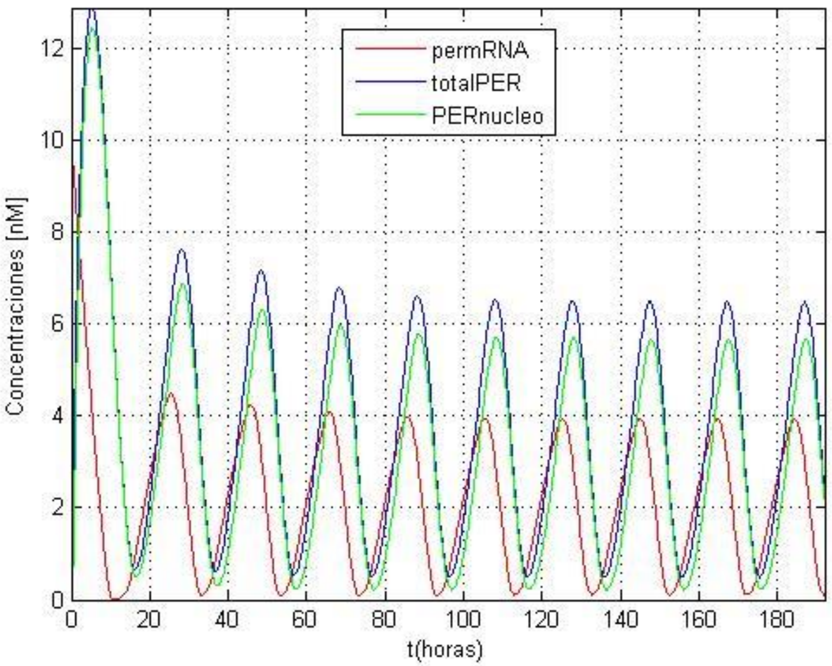
$$\frac{dB_N}{dt} = -V_{3B}\frac{B_N}{K_p + B_N} + V_{4B}\frac{B_{NP}}{K_{dp} + B_{NP}} + k_5 B_C - k_6 B_N - k_7 B_N PC_N + k_8 I_N - k_{dn} B_N \qquad \textbf{[14]}$$

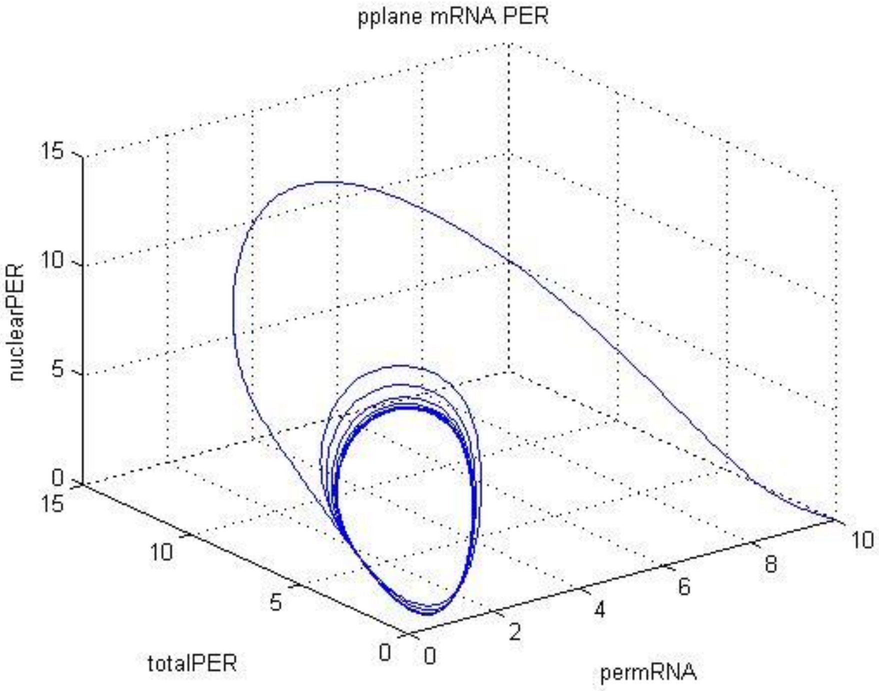
$$\frac{dB_{NP}}{dt} = V_{3B}\frac{B_N}{K_p + B_N} - V_{4B}\frac{B_{NP}}{K_{dp} + B_{NP}} - v_{dBN}\frac{B_{NP}}{K_d + B_{NP}} - k_{dn} B_{NP} \qquad \textbf{[15]}$$

$$\frac{dI_N}{dt} = -k_8 I_N + k_7 B_N PC_N - v_{dIN}\frac{I_N}{K_d + I_N} - k_{dn} I_N \qquad \textbf{[16]}$$

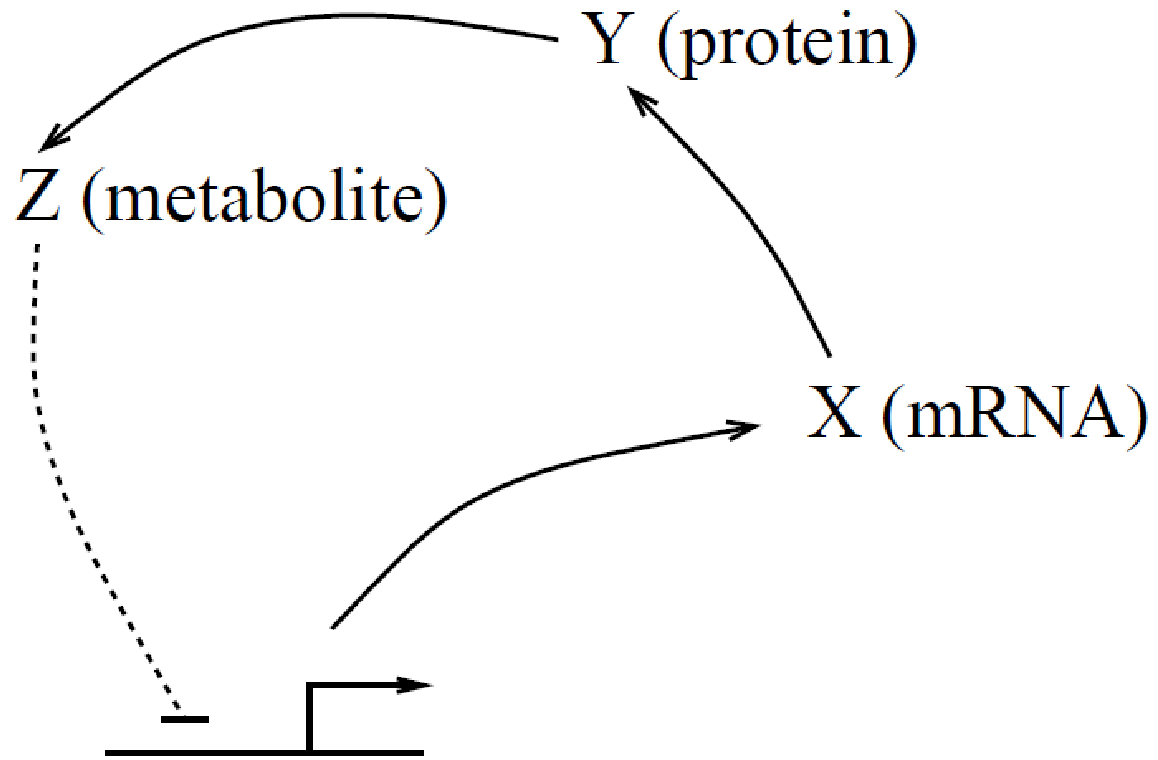

permRNA
totalPER
PERnucleo
Concentraciones [nM]
t(horas)


pplane mRNA PER
nuclearPER
totalPER
permRNA


permRNA
totalPER
PERnucleo
Concentraciones [nM]
t(horas)

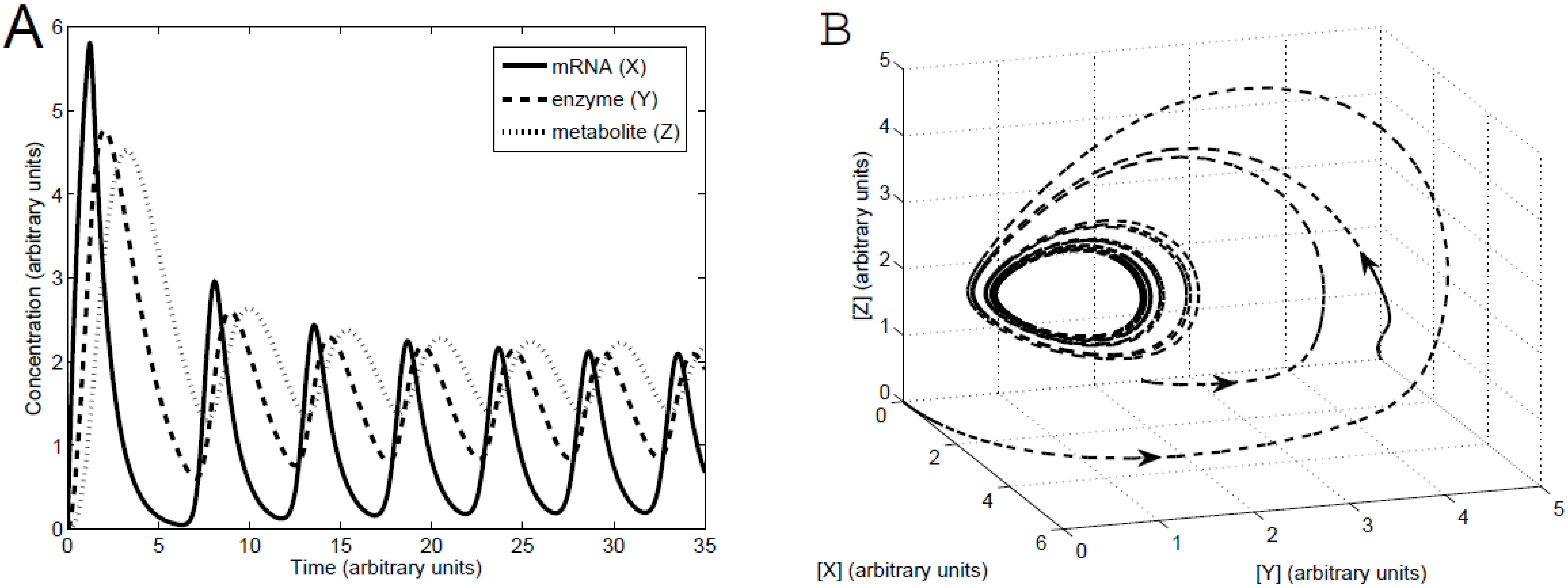

pplane mRNA PER
nuclearPER
totalPER
permRNA

El oscilador de Goodwin



Goodwin, B. C. (1965). Oscillatory behavior in enzymatic control processes. Advances in Enzyme Regulation, 3, 425–428.

$$\begin{aligned}
\frac{d}{dt}x(t) &= \frac{a}{k^n + (z(t))^n} - bx(t) \\
\frac{d}{dt}y(t) &= \alpha x(t) - \beta y(t) \\
\frac{d}{dt}z(t) &= \gamma y(t) - \delta z(t).
\end{aligned}$$

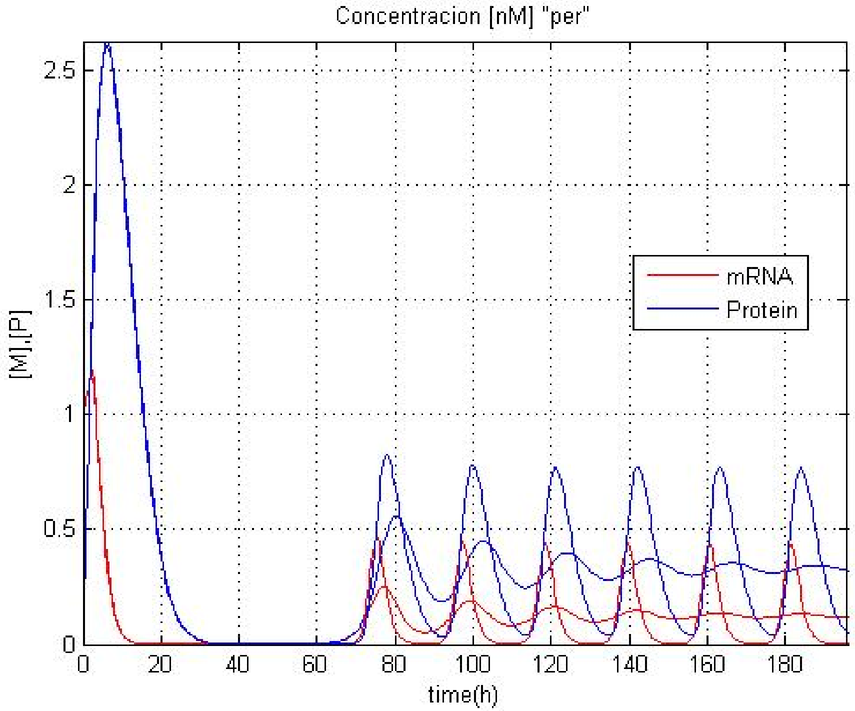


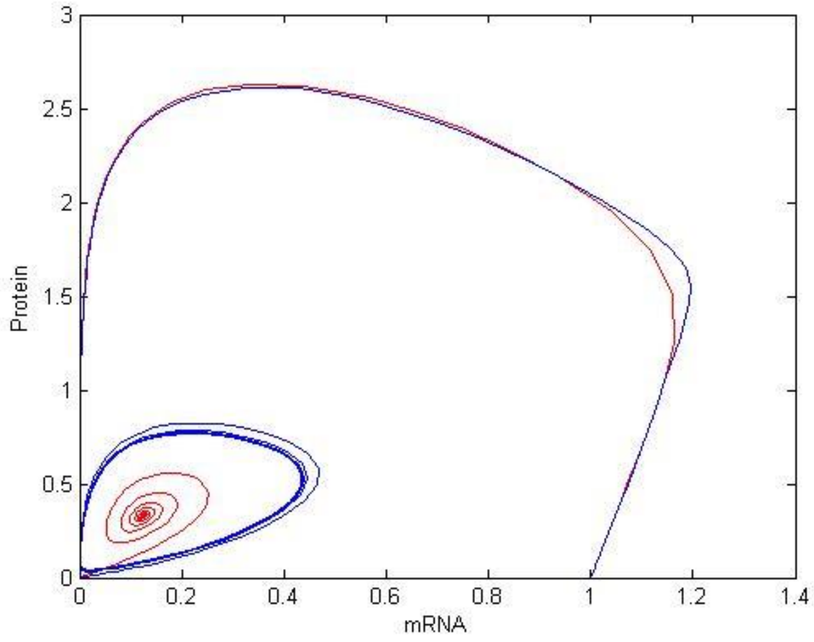
 Biophysical Journal Volume 89 July 2005 120–129

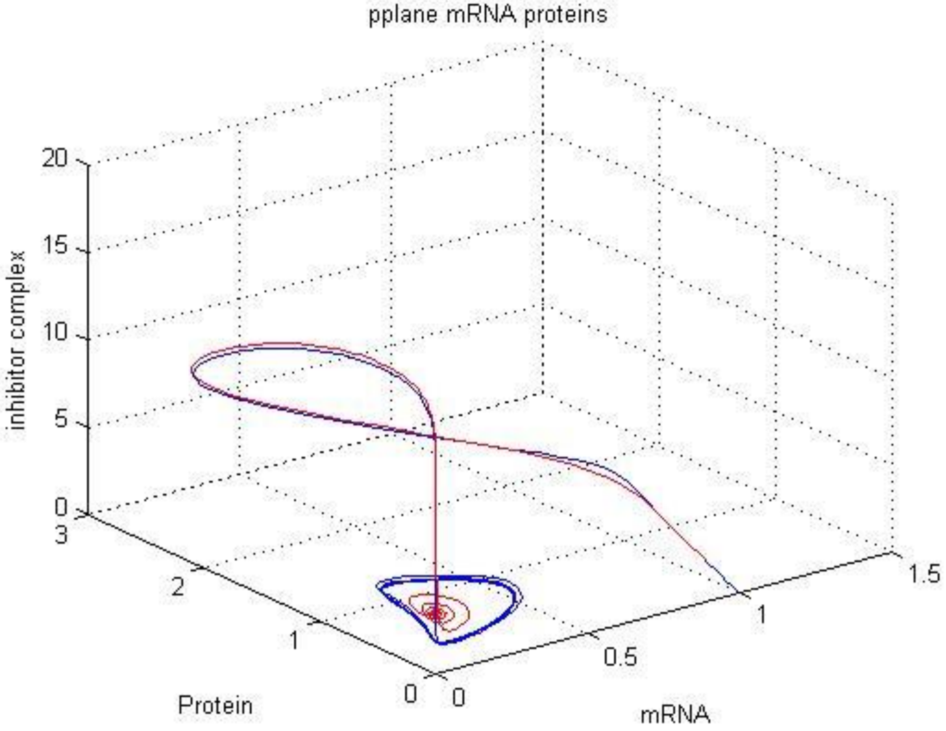
Spontaneous Synchronization of Coupled Circadian Oscillators

Didier Gonze,*† Samuel Bernard,* Christian Waltermann,* Achim Kramer,‡ and Hanspeter Herzel*
*Institute for Theoretical Biology, Humboldt Universität zu Berlin, Berlin, Germany; †Unité de Chronobiologie Théorique, Université Libre de Bruxelles, Brussels, Belgium; and ‡Laboratory of Chronobiology, Institute of Medical Immunology, Charité-Universitätsmedizin Berlin, Berlin, Germany

$$\frac{dX}{dt} = v_1 \frac{K_1^n}{K_1^n + Z^n} - v_2 \frac{X}{K_2 + X}$$
$$\frac{dY}{dt} = k_3 X - v_4 \frac{Y}{K_4 + Y},$$
$$\frac{dZ}{dt} = k_5 Y - v_6 \frac{Z}{K_6 + Z}.$$



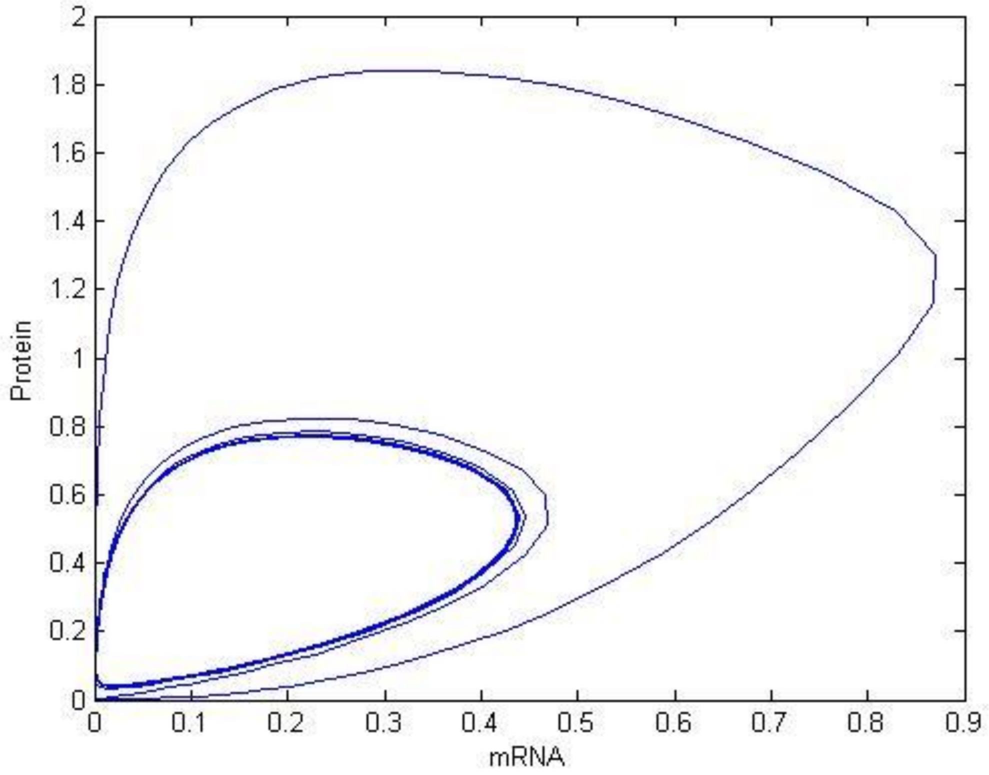




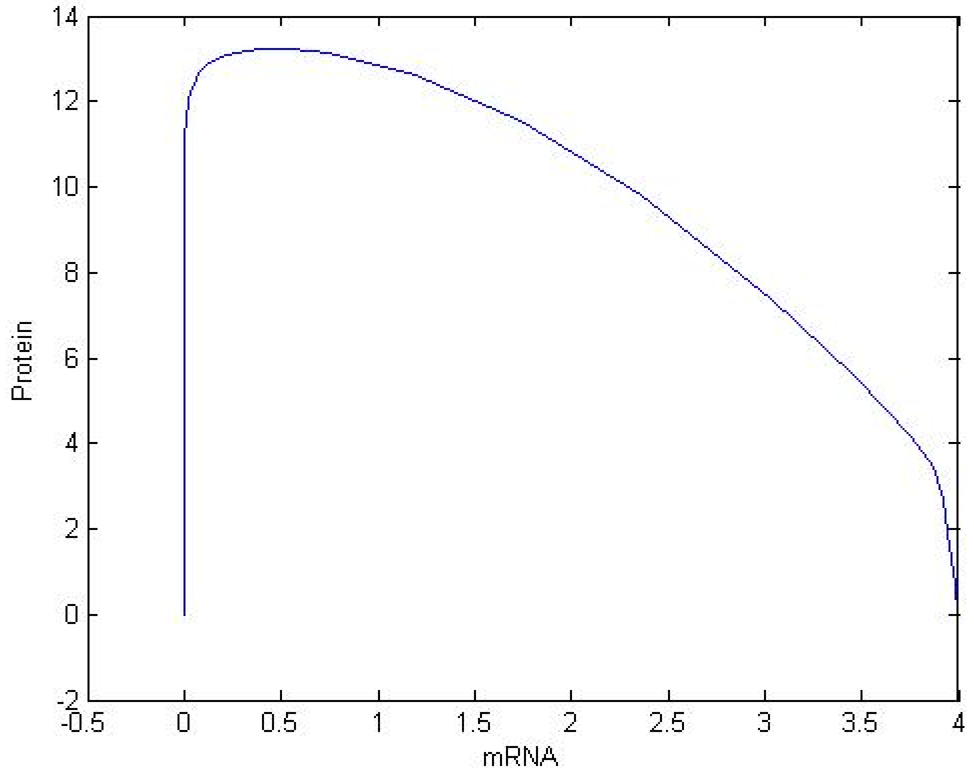
Con n=4 punto fijo atractor -------

Con n=10 ciclo limite -------

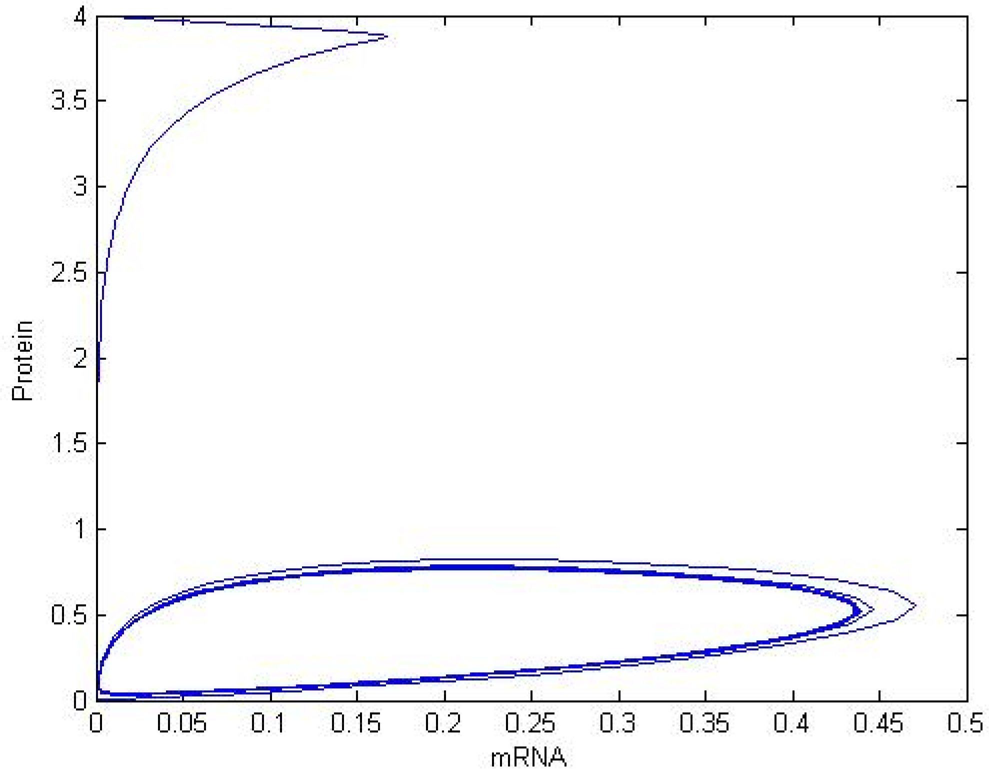
Modelo sensible a condiciones iniciales de mRNA



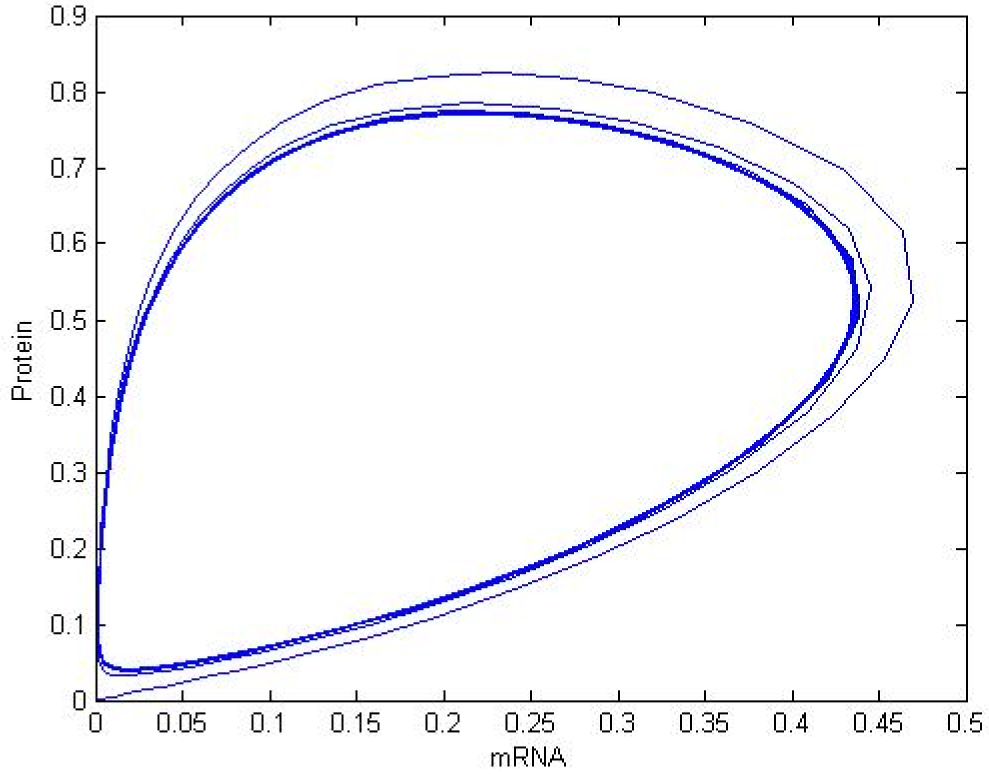
M(t=0)=0, P(t=0)=0, IC(t=0)=0



M(t=0)=4, P(t=0)=0, IC(t=0)=0



M(t=0)=0, P(t=0)=4, IC(t=0)=0



M(t=0)=0, P(t=0)=0, IC(t=0)=4

Oscilador circadiano estocástico

Documentos de apoyo:

Stochastic models for circadian rhythms: effect of molecular noise on periodic and chaotic behaviour

Didier Gonze, José Halloy, Jean-Christophe Leloup, Albert Goldbeter *

Unité de chronobiologie théorique, faculté des sciences, université libre de Bruxelles, Campus Plaine, CP 231, B1050 Brussels, Belgium

Stochastic simulations

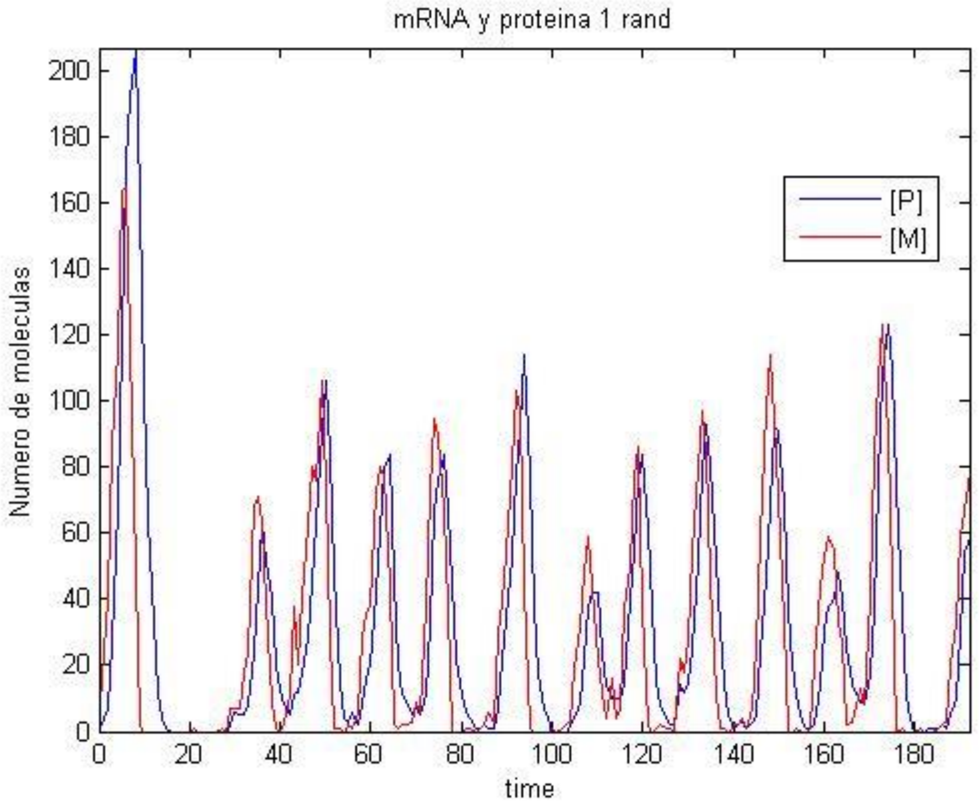
Application to biomolecular networks

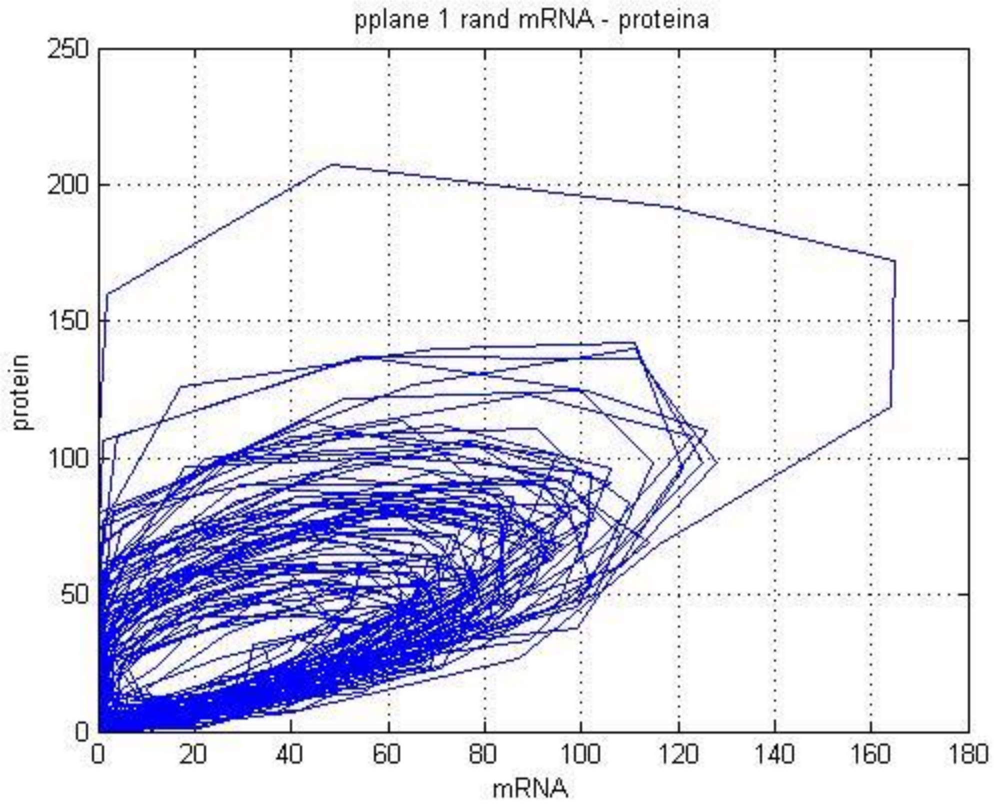
Didier Gonze and Adama Ouattara

$$\frac{dX}{dt} = v_s \frac{X}{K_M + X} - k_d X$$

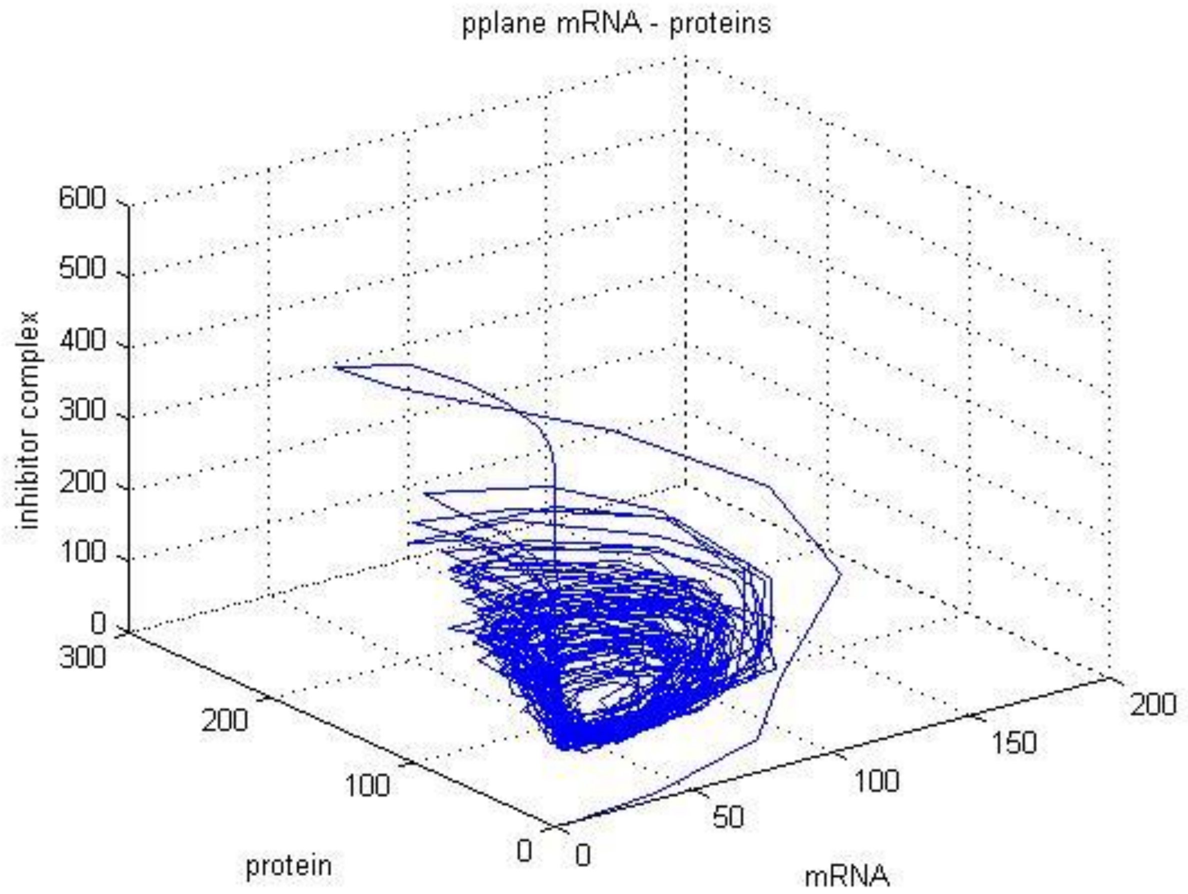
process	reaction	propensity
synthesis	$\rightarrow X$	$w_1 = v_s \Omega \frac{X}{K_M \Omega + X}$
degradation	$X \rightarrow$	$w_2 = k_d X$

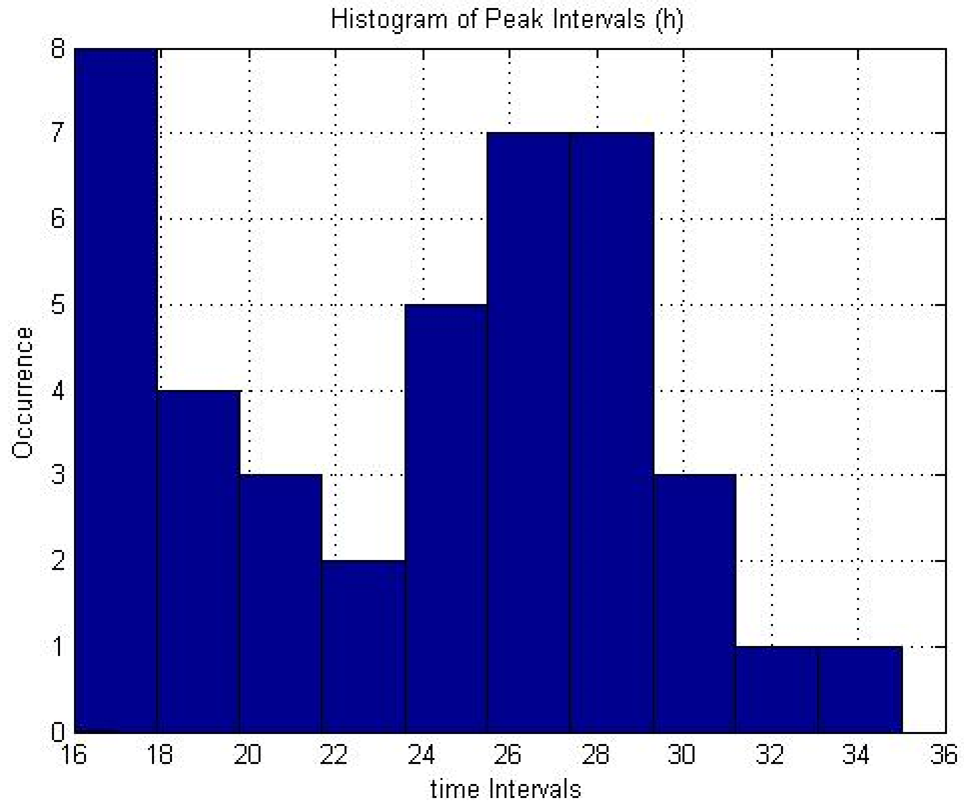
n=4, Ω=100, tiempo final=1000



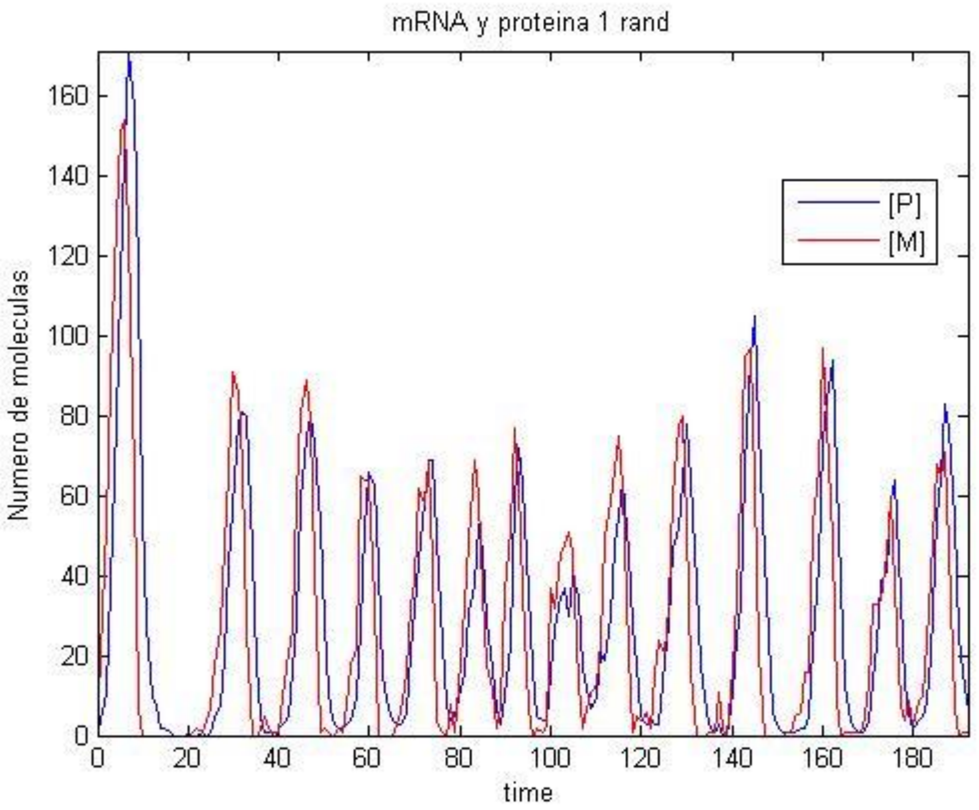


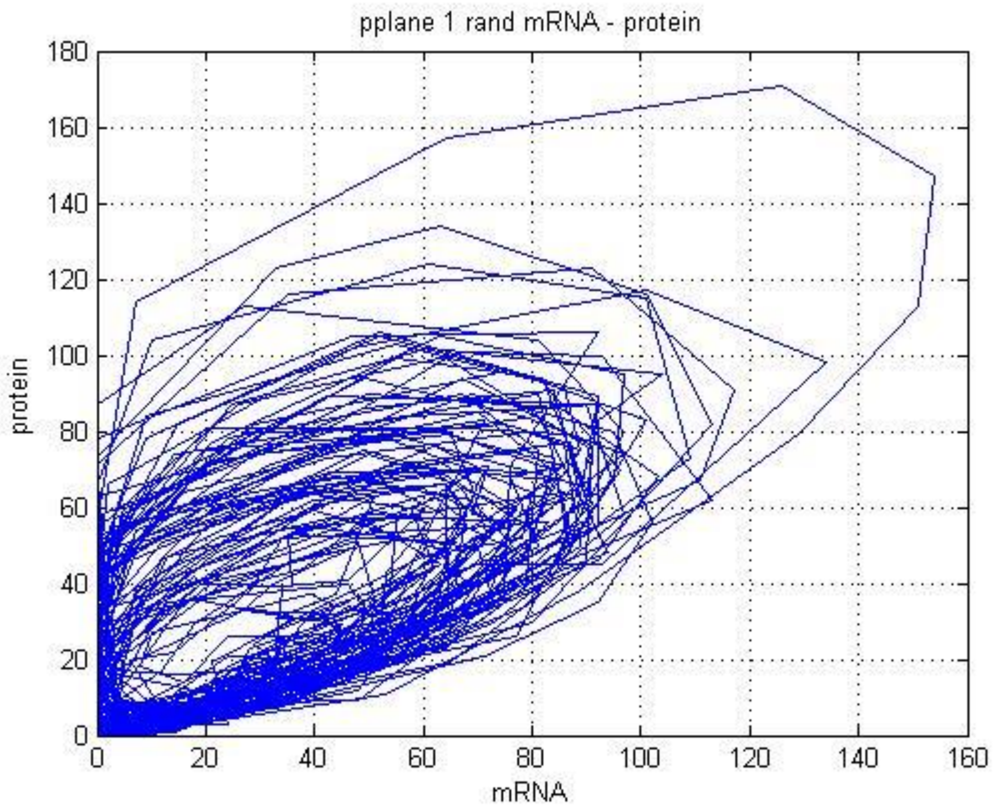
n=4, Ω=100, tiempo final=1000



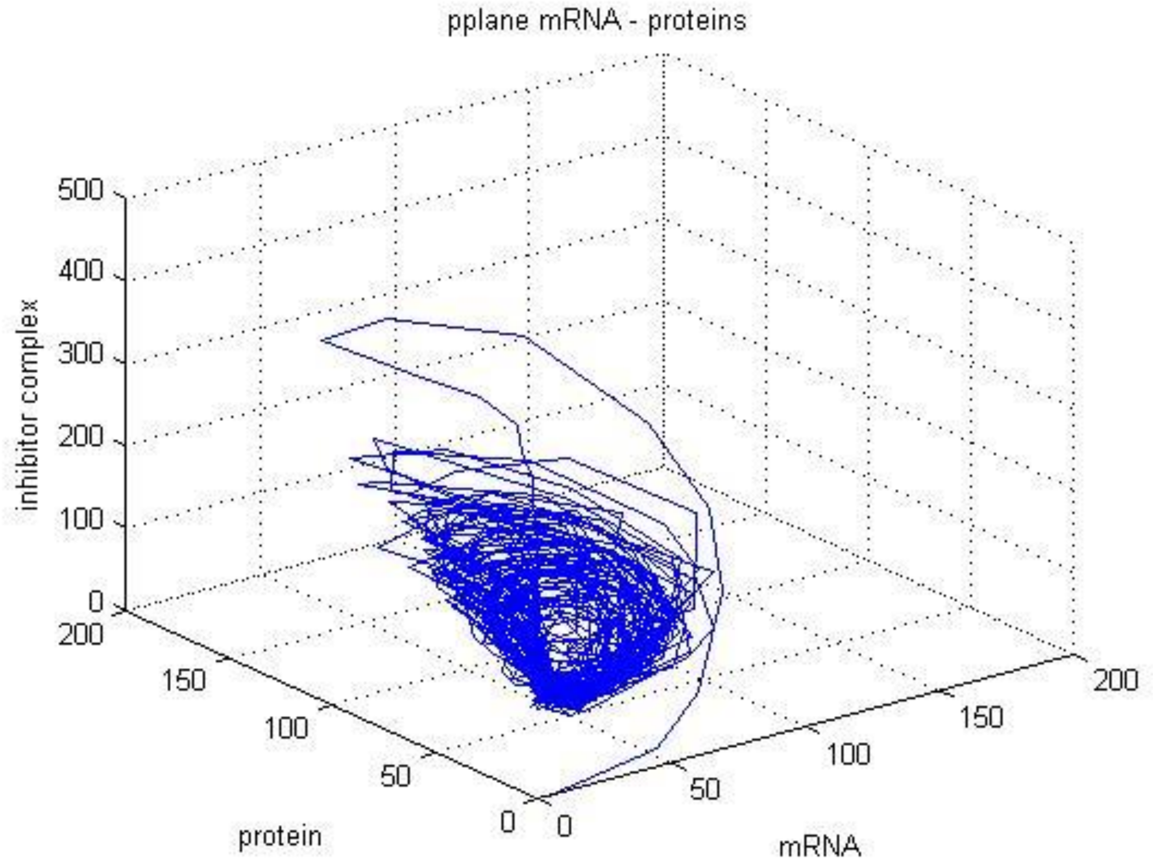


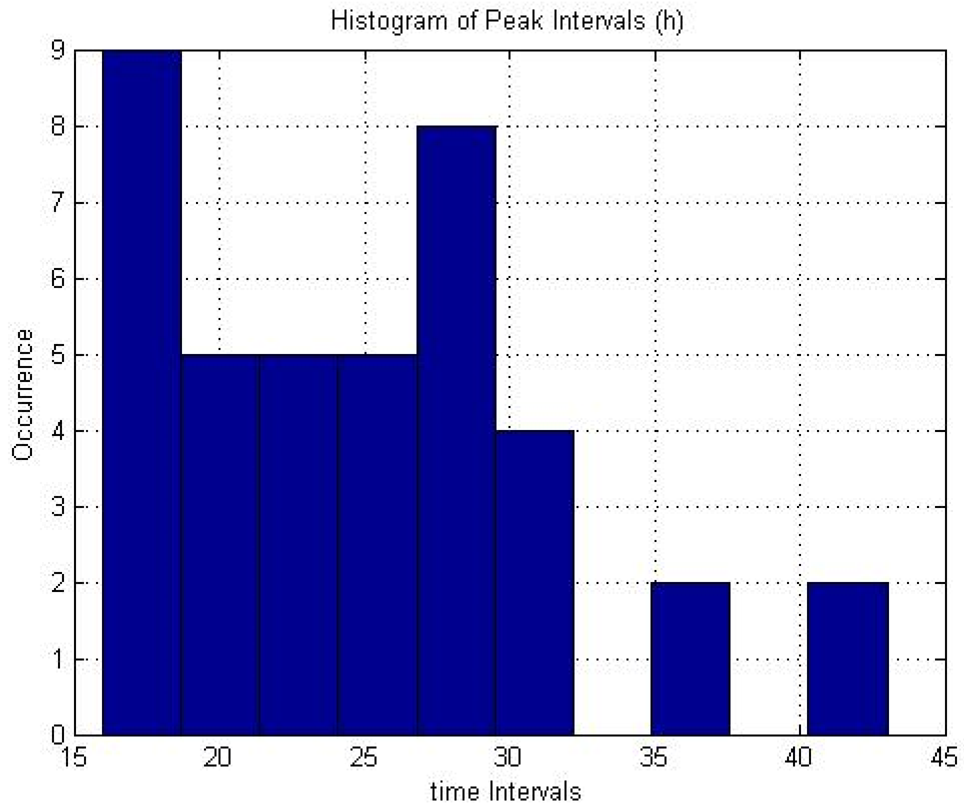
n=4, Ω=100, tiempo final=1000



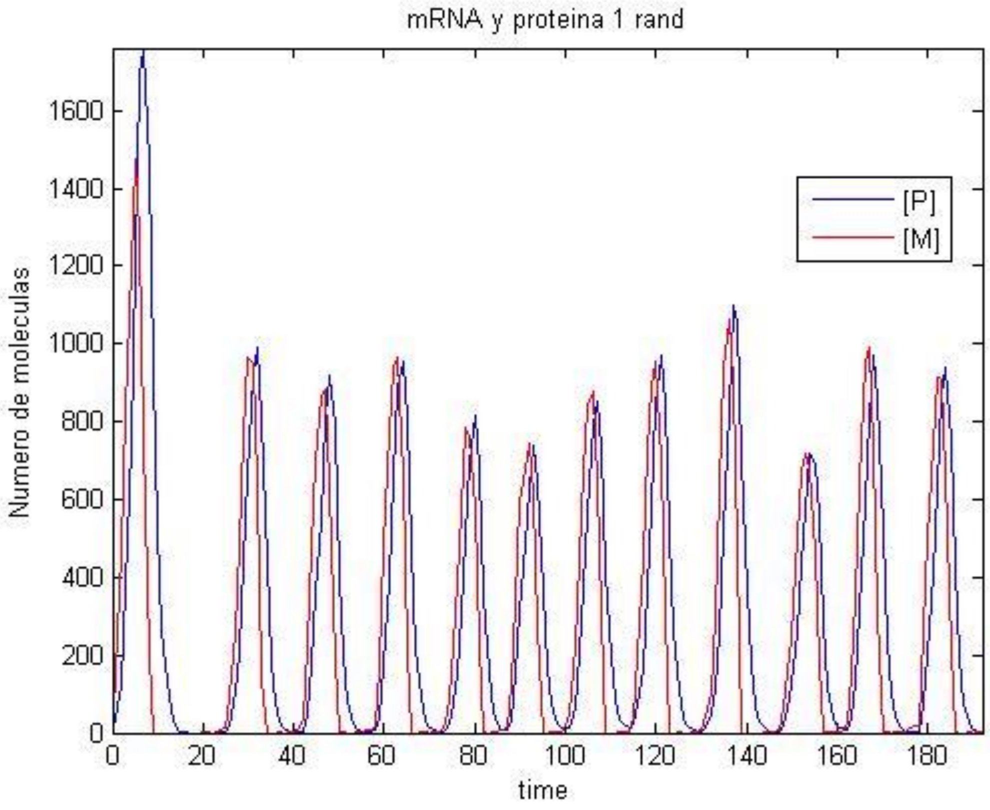


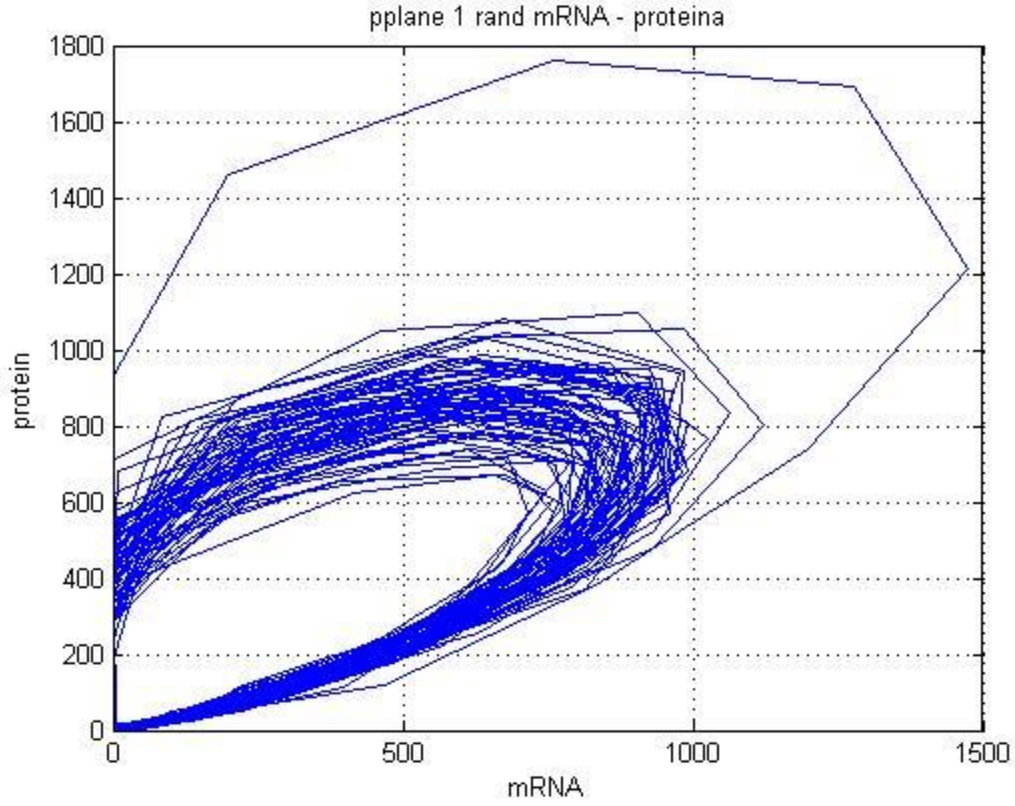
n=4, Ω=100, tiempo final=1000



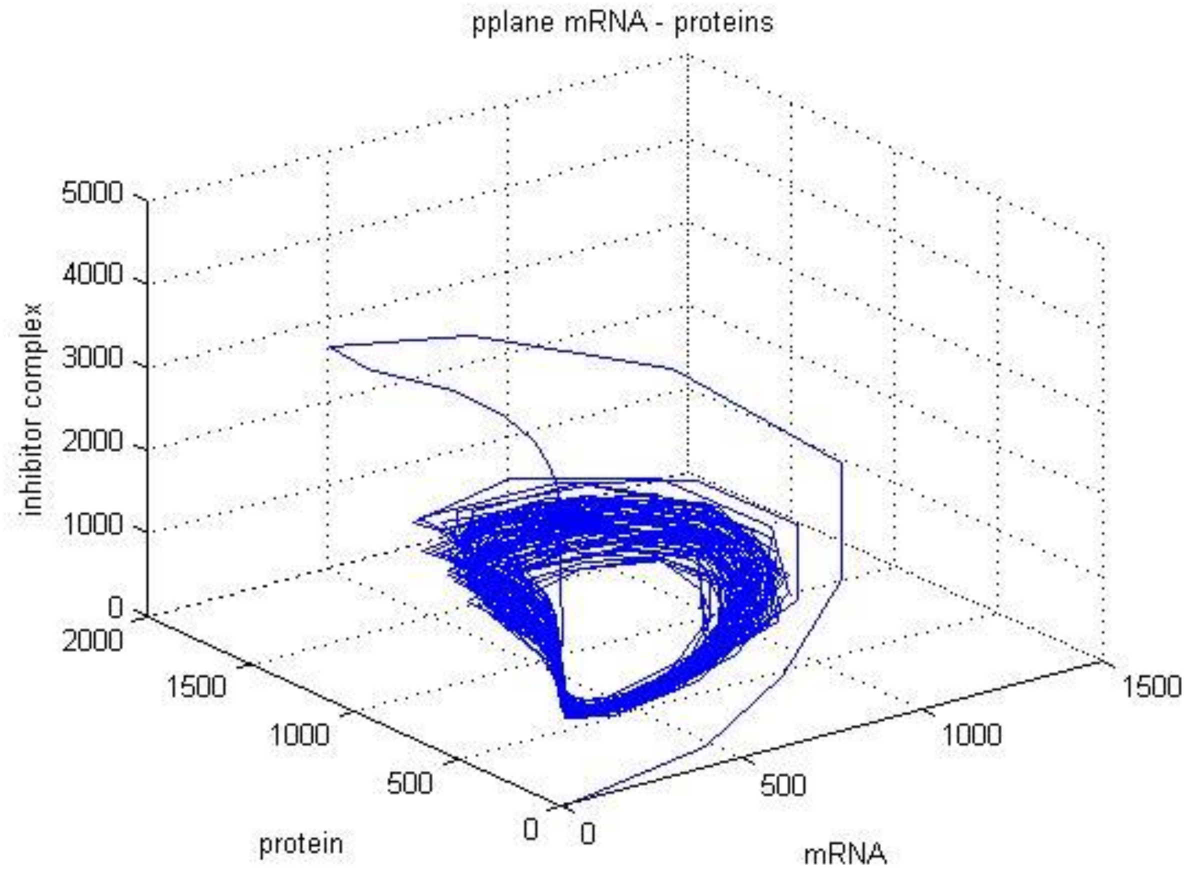


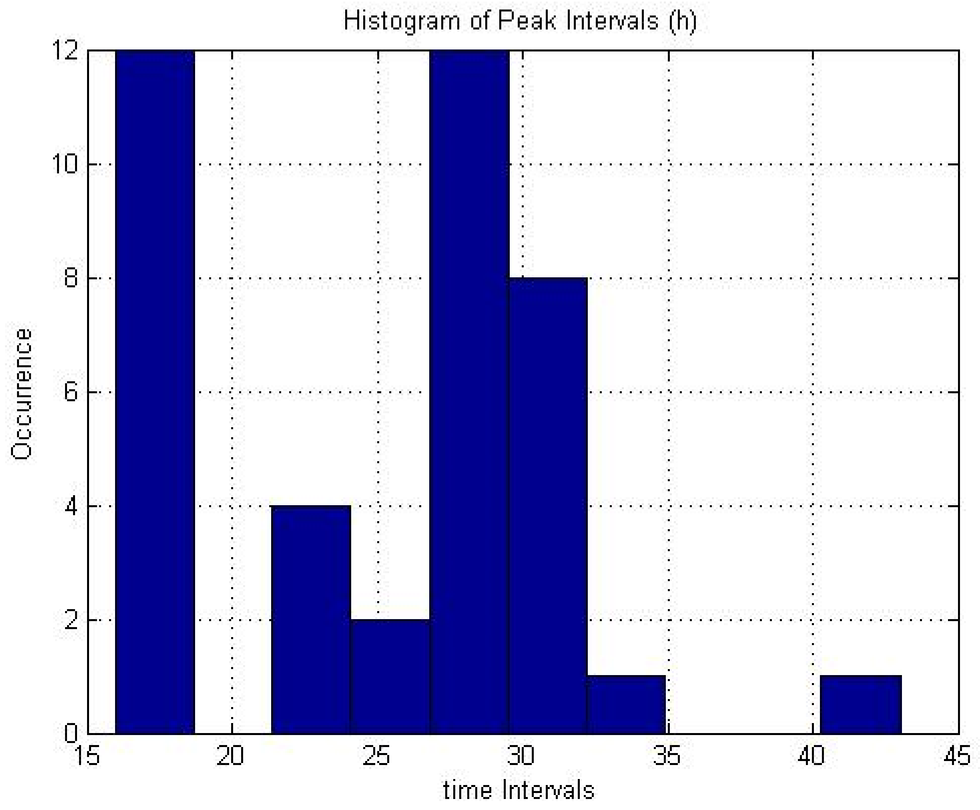
n=4, Ω=1000, tiempo final=1000



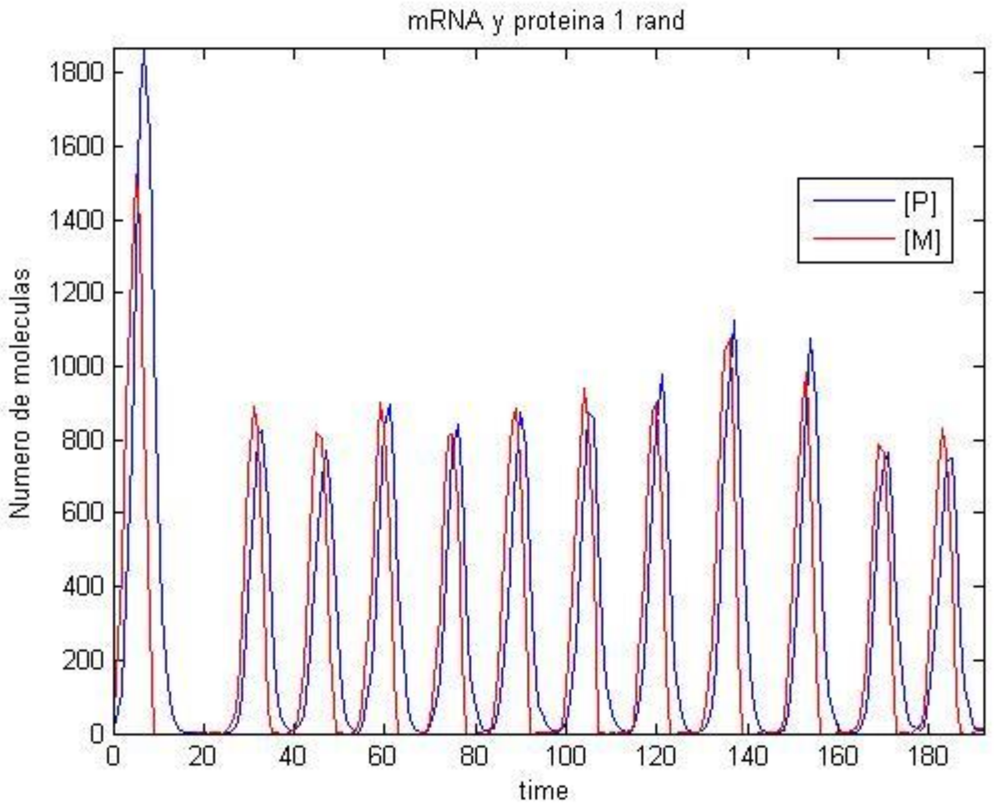


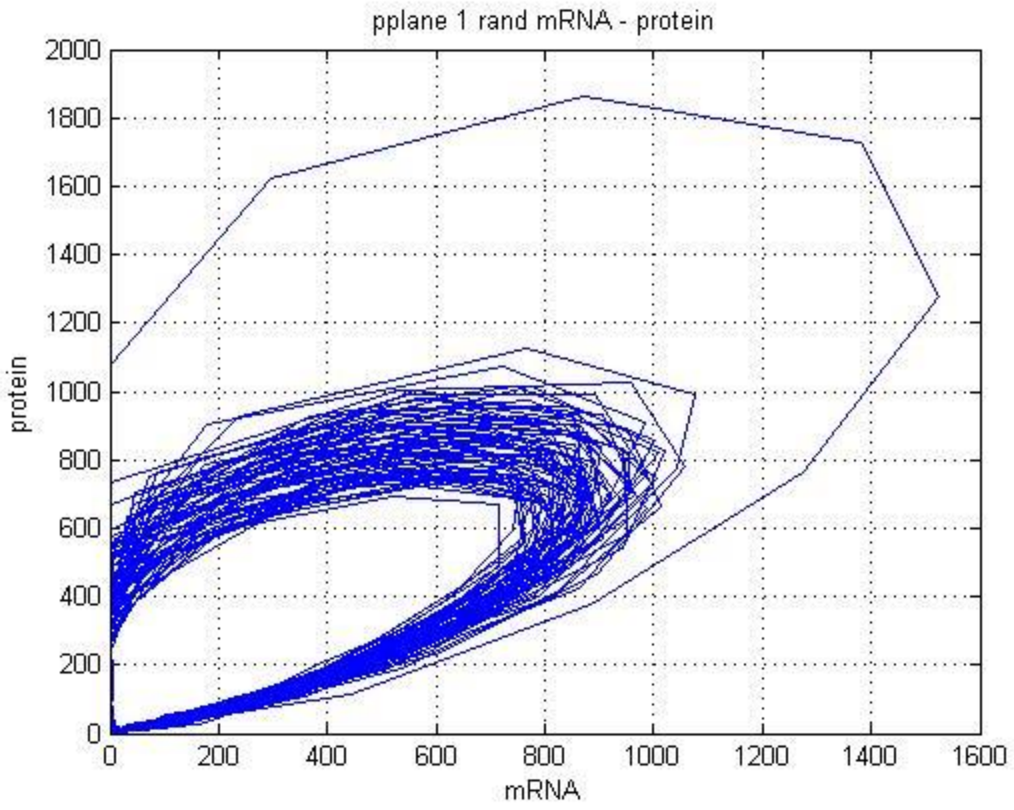
n=4, Ω=1000, tiempo final=1000



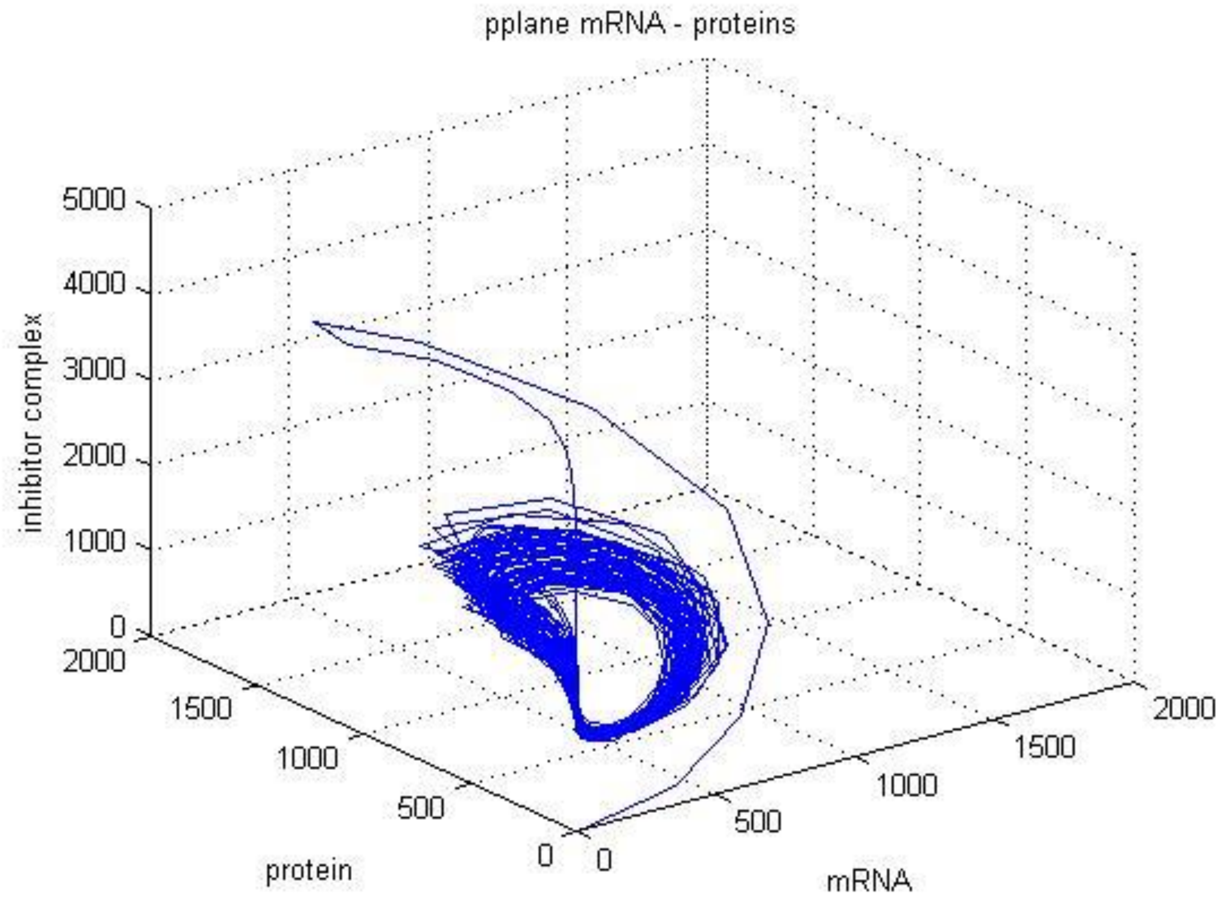


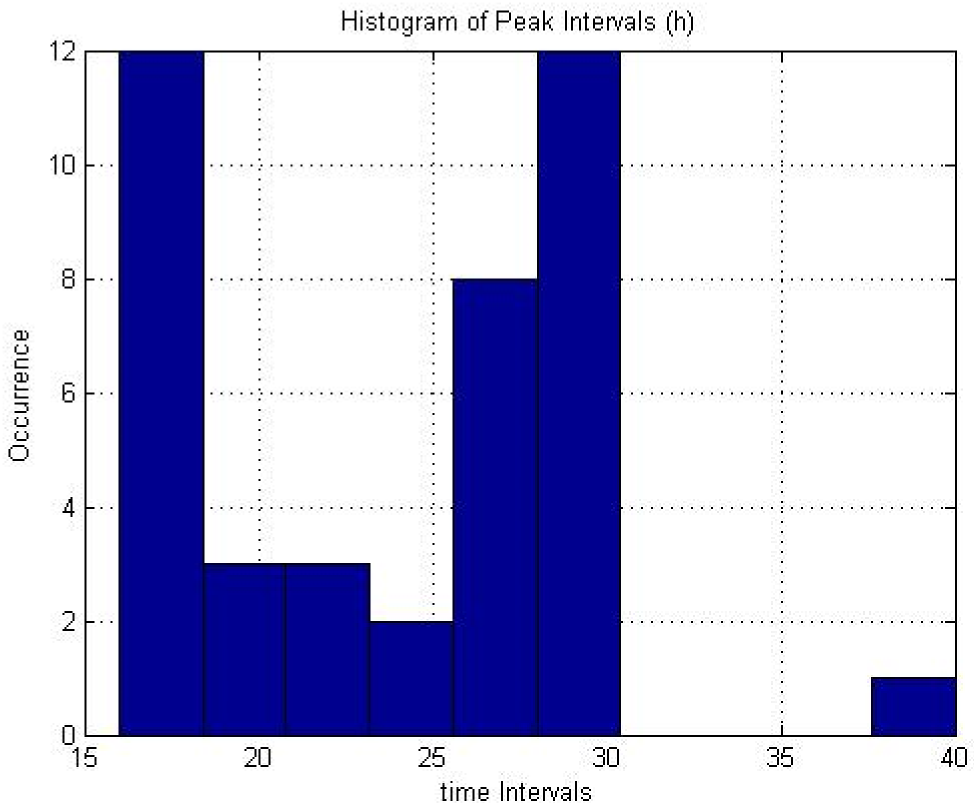
n=4, Ω=1000, tiempo final=1000



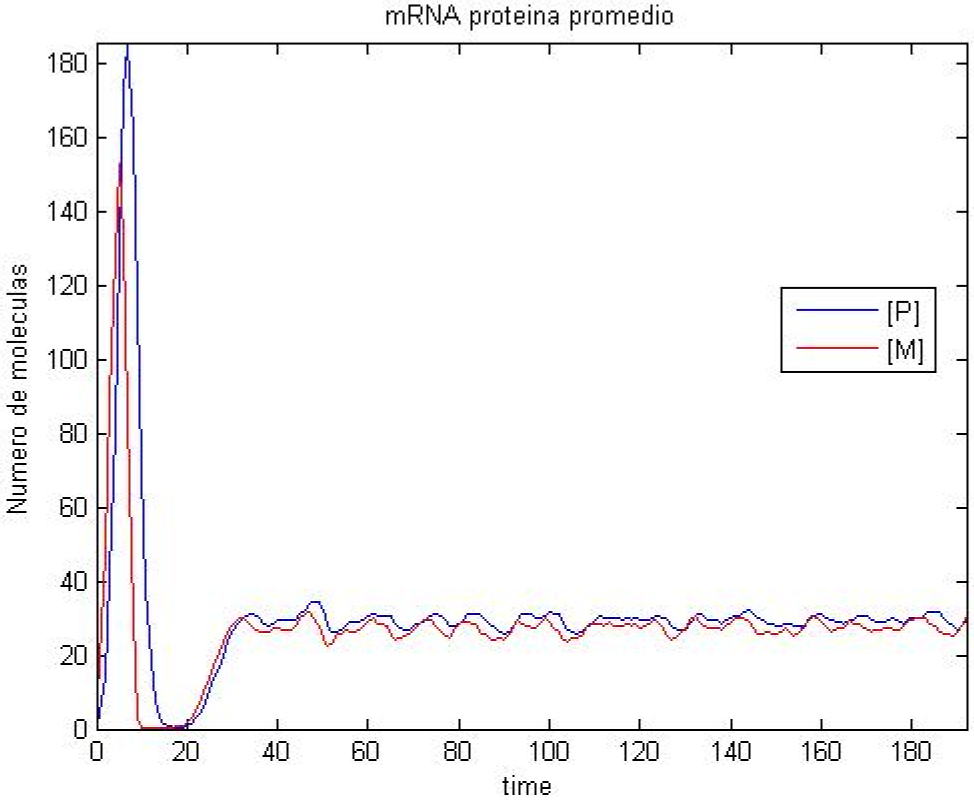


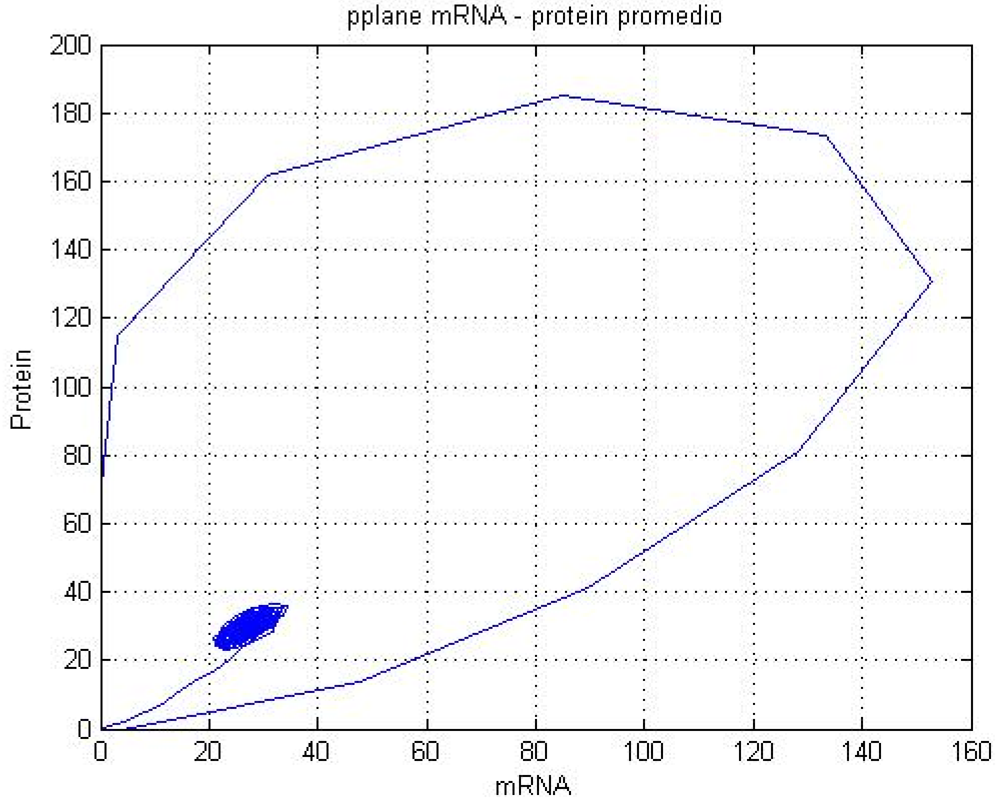
n=4, Ω=1000, tiempo final=1000



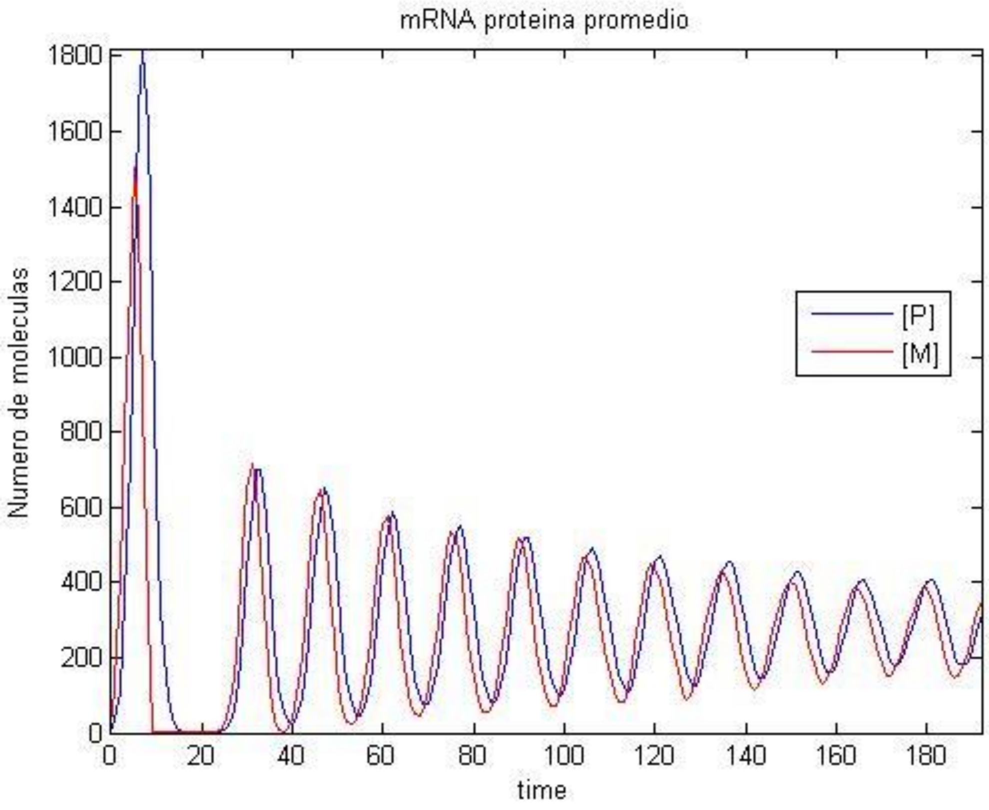


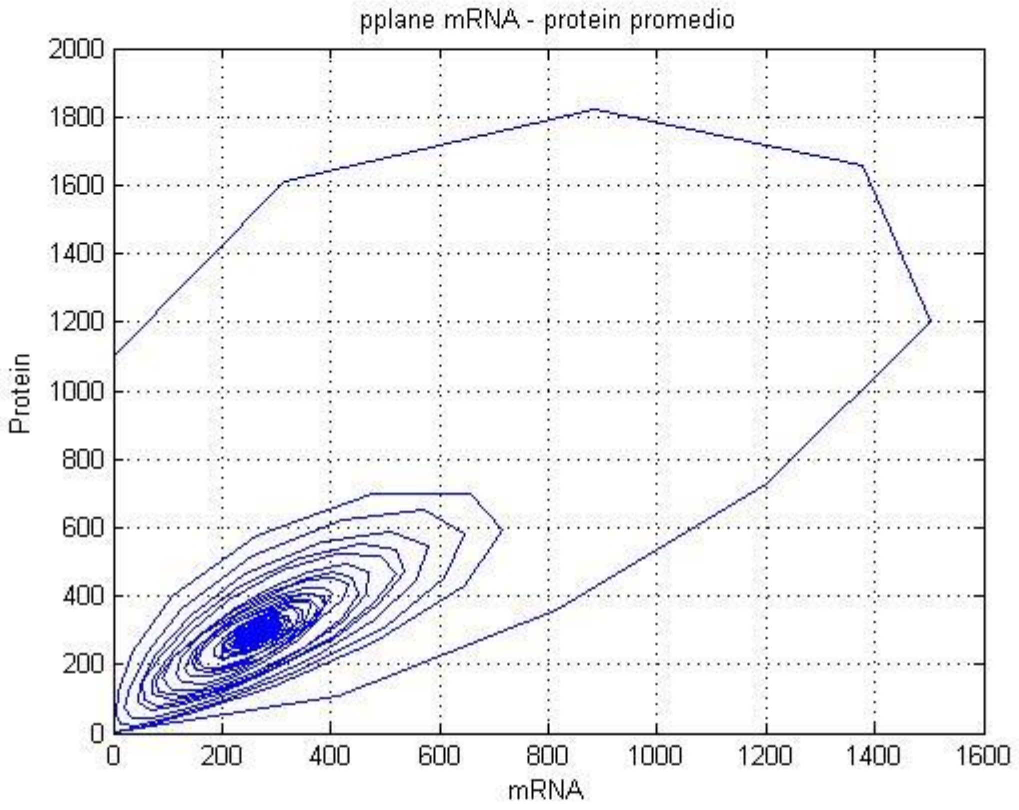
n=4, Ω=100, tiempo final=1000

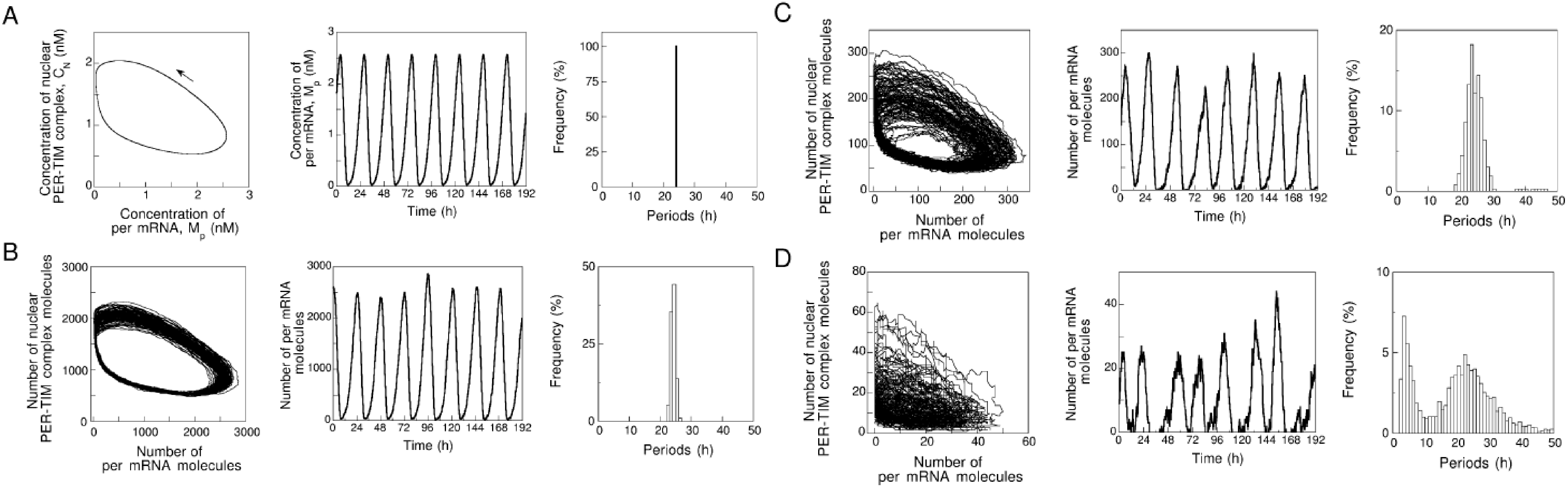




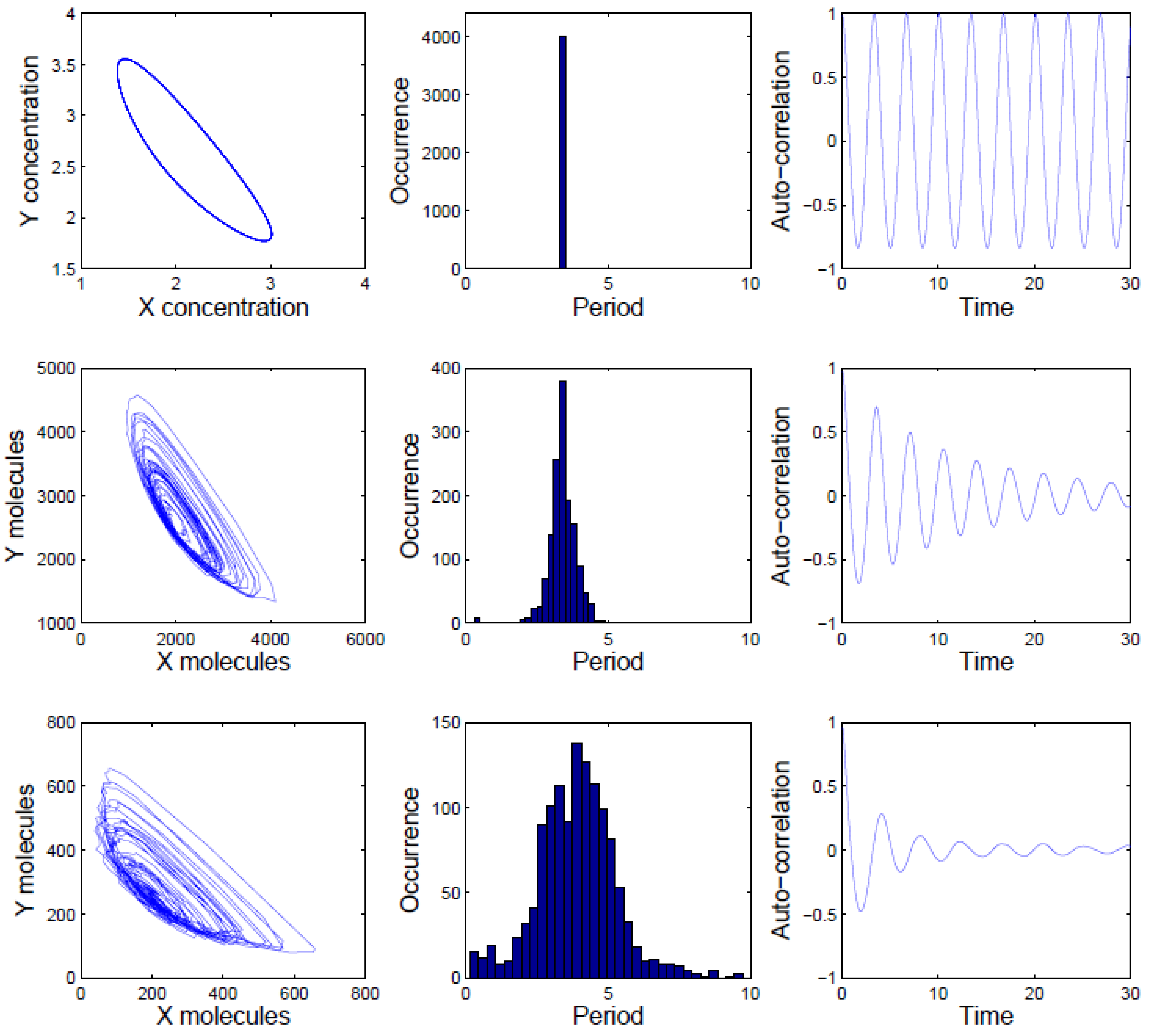
n=4, Ω=1000, tiempo final=1000





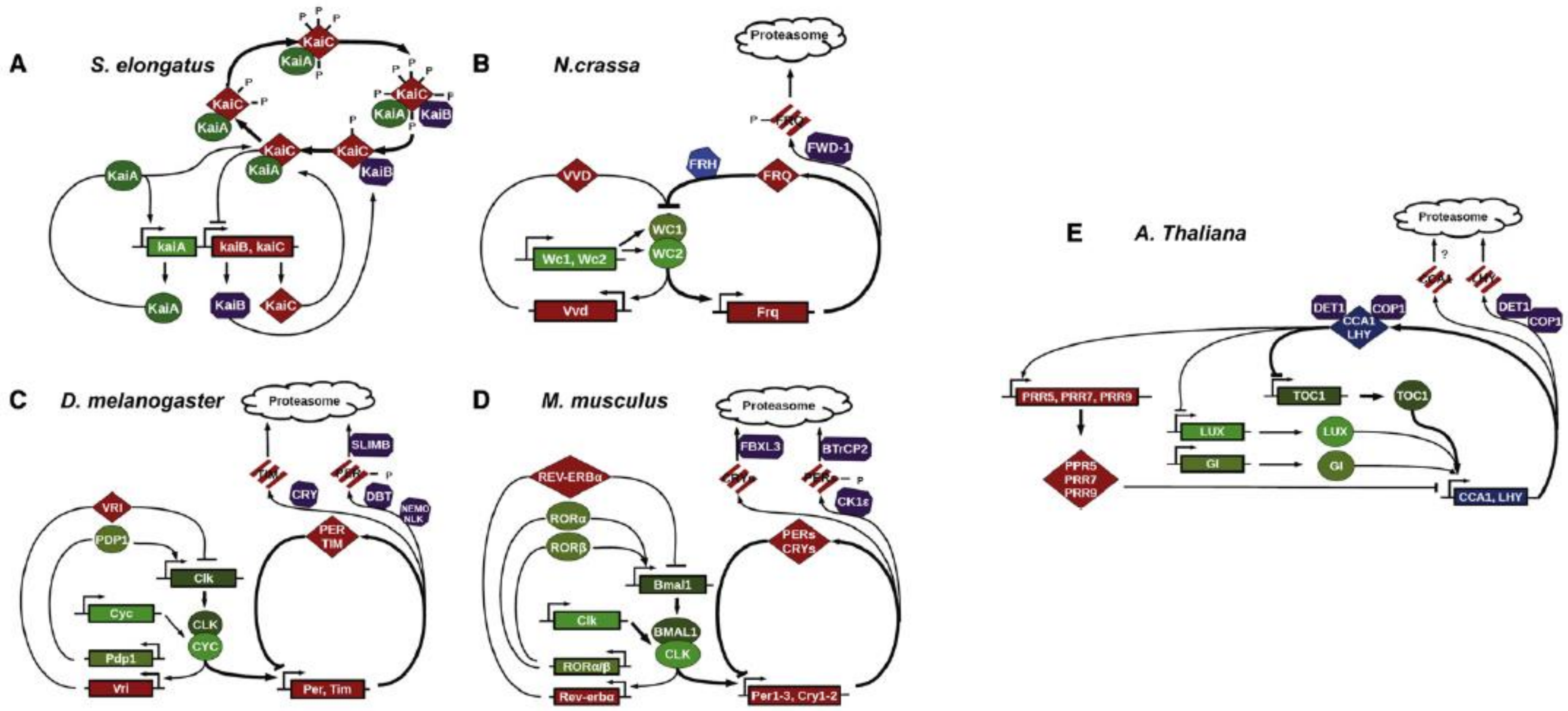

A
Concentration of nuclear PER-TIM complex, C_N (nM)
Concentration of per mRNA, M_p (nM)
Concentration of per mRNA, M_p (nM)
Time (h)
Frequency (%)
Periods (h)
B
Number of nuclear PER-TIM complex molecules
Number of per mRNA molecules
Number of per mRNA molecules
Time (h)
Frequency (%)
Periods (h)
C
Number of nuclear PER-TIM complex molecules
Number of per mRNA molecules
Number of per mRNA molecules
Time (h)
Frequency (%)
Periods (h)
D
Number of nuclear PER-TIM complex molecules
Number of per mRNA molecules
Number of per mRNA molecules
Time (h)
Frequency (%)
Periods (h)

The Brusselator (proposed in 1967 in Brussels by R. Lefever I. Prigogine et G. Nicolis)



(Re)inventing the Circadian Feedback Loop

Steven A. Brown,[1,*] Elzbieta Kowalska,[1] and Robert Dallmann[1]
[1]Institute of Pharmacology and Toxicology, University of Zürich, Winterthurerstrasse 190, 8057 Zurich, Switzerland



Software

- StochSS - A cloud computing framework for modeling and simulation of stochastic biochemical systems
- StochKit2 - Stochastic simulation kit
- Cain - Stochastic simulation of chemical kinetics. Direct, next reaction, tau-leaping, hybrid, etc.
- StochPy - Stochastic modelling in Python
- SynBioSS - Stochastic simulation of chemical kinetics using the exact SSA as well as an SSA/Langevin hybrid. Both MPI-parallel (supercomputer) and GUI (desktop) versions are provided.
- GillespieSSA - R package for Gillespie algorithm
- [1] - Mathematica code and applet for stochastic simulation of chemical kinetics.
- pSSAlib - C++ implementations of all partial-propensity methods.
- Gillespie.jl- Julia implementation of Gillespie's direct method