Gillespie

- Step 0: set up S,P,K
- Step 1: Calculate

a_r $\quad a_0 = \text{sum}(a_r)$

- Step 2: Use 2 random numbers to pick when the next event occurs and which reaction it is.

$$\tau = \frac{1}{a_0}\ln\left(\frac{1}{p_1}\right) \qquad \sum_{i=1}^{r-1} a_i < p_2 a_0 < \sum_{i=1}^{r} a_i$$

- Step 3: update system for the one reaction only

Tau-leap

- Step 0: set up S,P,K
- Step 1: Calculate

a_r

$$\lambda_r = a_r \Delta t \qquad P(n) = \frac{\lambda_r{}^n e^{-\lambda_r}}{n!}$$

(adjust time step until OK)

- Step 2: use R random numbers p_r to determine number of events, n_r , for each reaction.

$$\sum_{i=1}^{n_r-1} P(i) < p_r < \sum_{i=1}^{n_r} P(i)$$

- Step 3: update system for all R reactions

Three Ways to Simulate a Poisson Process:

- Match time step to next event (1 event)
  - **Gillespie's "exact" algorithm**
  - Always accurate, but moderately expensive

- Take medium time steps (0 to ~20 events)
  - **"Tau-leap" algorithm**
  - Accurate if system doesn't change significantly in a time step; less expensive

- Take large time steps (> 10 events)
  - **Gillespie's "Chemical Langevin Equation" algorithm**
  - Accurate if system doesn't change significantly in a time step, but > 10 events occur. Least expensive

Concentrations vs Numbers

For monomolecular reaction, $k_\mu = c_u$

For two molecular reaction, $k_\mu = Vc_u$ $\quad$ $k_\mu = Vc_u/2$

For three molecular reaction, $k_\mu = V^2 c_u$

Comments on Assignment 9

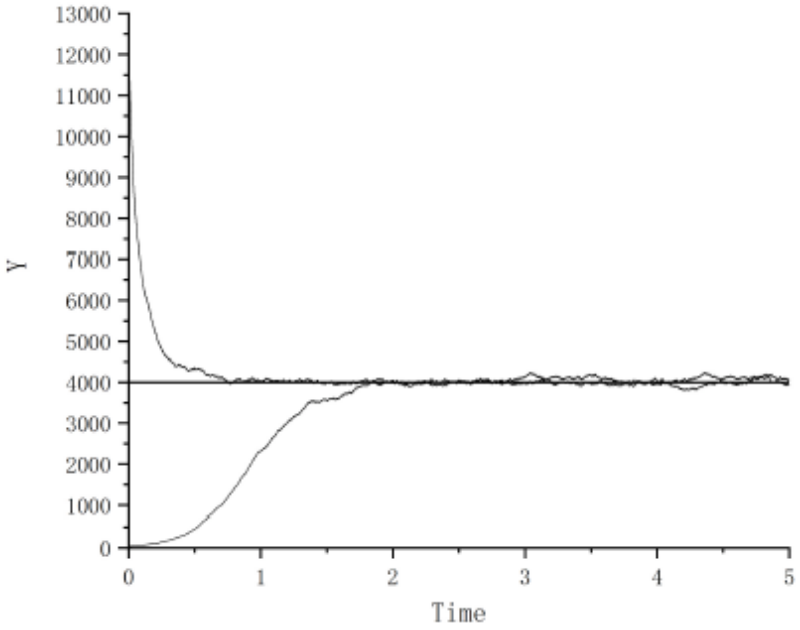


图 1: SSA

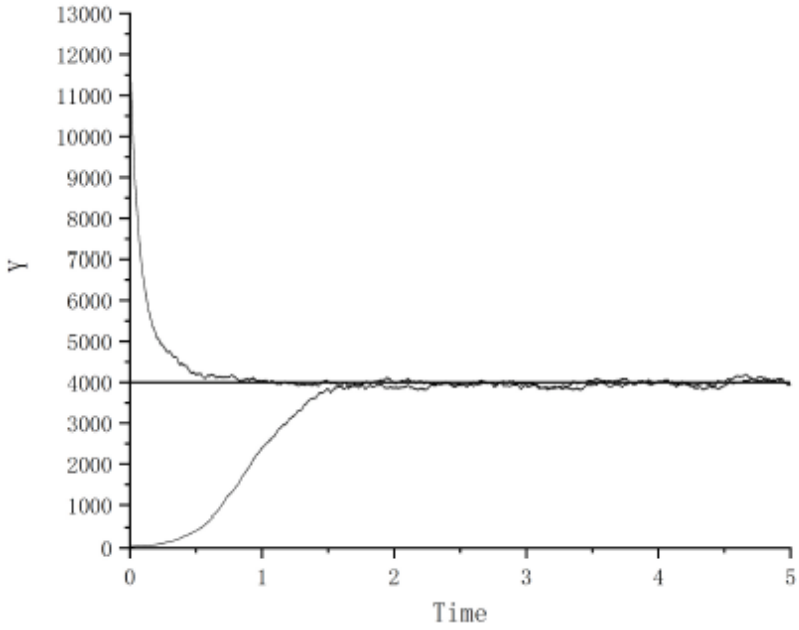


图 2: Tau-leap

Chap4-3 Effects of noise on the dynamics of biological networks

1. Robustness of circadian rhythms with respect to molecular noise

2. A genetic timer through noise-induced stabilization of an unstable state

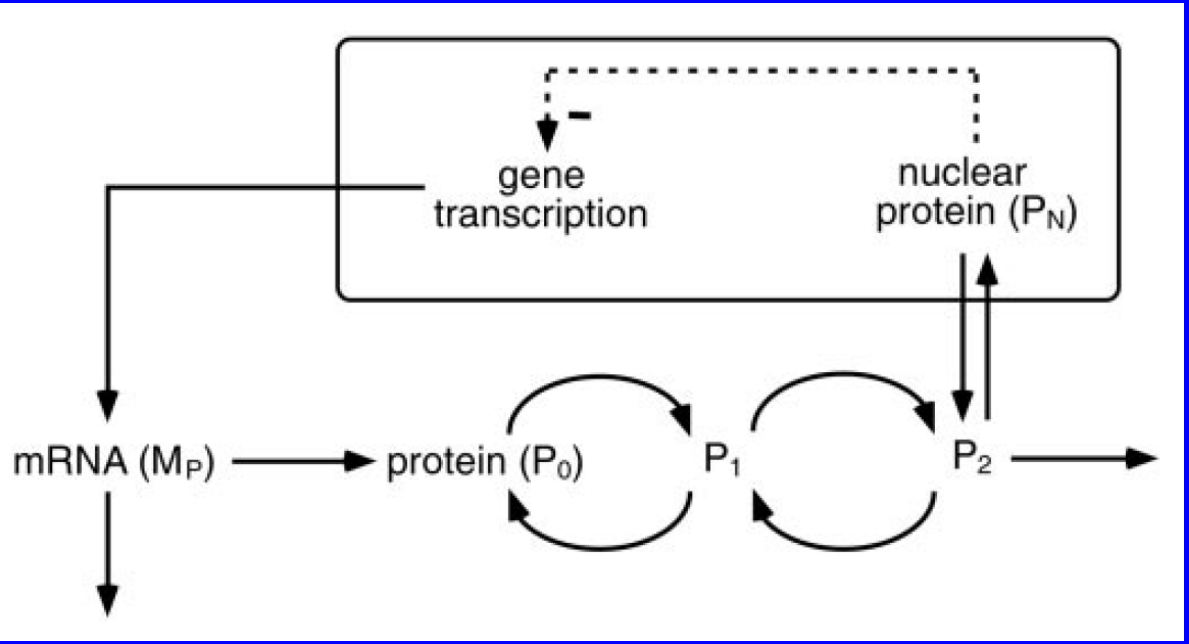
3. Enhancement of internal-noise coherence resonance by modulation of external noise in a circadian oscillator

1. Robustness of circadian rhythms with respect to molecular noise

We use a core molecular model capable of generating circadian rhythms to assess the robustness of circadian oscillations with respect to molecular noise. The model is based on the negative feedback exerted by a regulatory protein on the expression of its gene.

Gonze, D., J. Halloy, et al. (2002). PNAS **99**(2): 673-678.

Core Molecular Model for Circadian Oscillations



PER
FRQ

The model incorporates gene transcription into mRNA, translation of mRNA into protein, reversible phosphorylation leading to degradation of the protein, transport of the latter into the nucleus, and repression of gene expression by the nuclear form of the protein.

Kinetic Equations of the Deterministic Model

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

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

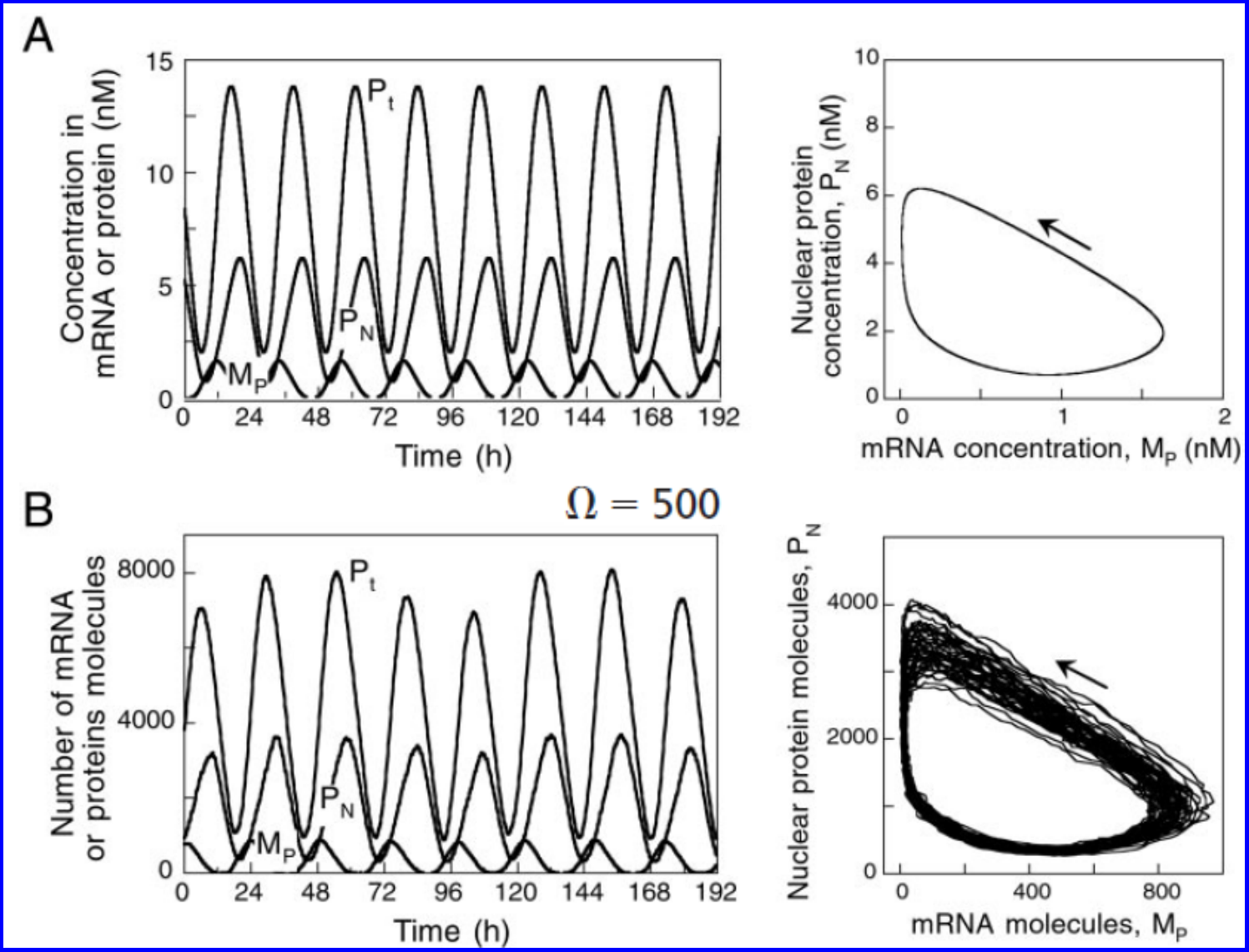
$$\frac{dP_1}{dt} = v_1 \frac{P_0}{K_1 + P_0} - v_2 \frac{P_1}{K_2 + P_1} - v_3 \frac{P_1}{K_3 + P_1} + v_4 \frac{P_2}{K_4 + P_2}$$

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

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

Decomposition of the Deterministic Model into Elementary Reaction Steps

Reaction number	Reaction step	Probability of reaction
1	$G + P_N \xrightarrow{a_1} GP_N$	$w_1 = a_1 \times G \times P_N / \Omega$
2	$GP_N \xrightarrow{d_1} G + P_N$	$w_2 = d_1 \times GP_N$
3	$GP_N + P_N \xrightarrow{a_2} GP_{N2}$	$w_3 = a_2 \times GP_N \times P_N / \Omega$
4	$GP_{N2} \xrightarrow{d_2} GP_N + P_N$	$w_4 = d_2 \times GP_{N2}$
5	$GP_{N2} + P_N \xrightarrow{a_3} GP_{N3}$	$w_5 = a_3 \times GP_{N2} \times P_N / \Omega$
6	$GP_{N3} \xrightarrow{d_3} GP_{N2} + P_{N3}$	$w_6 = d_3 \times GP_{N3}$
7	$GP_{N3} + P_N \xrightarrow{a_4} GP_{N4}$	$w_7 = a_4 \times GP_{N3} \times P_N / \Omega$
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	$P_N \xrightarrow{k_2} P_2$	$w_{30} = k_2 \times P_N$



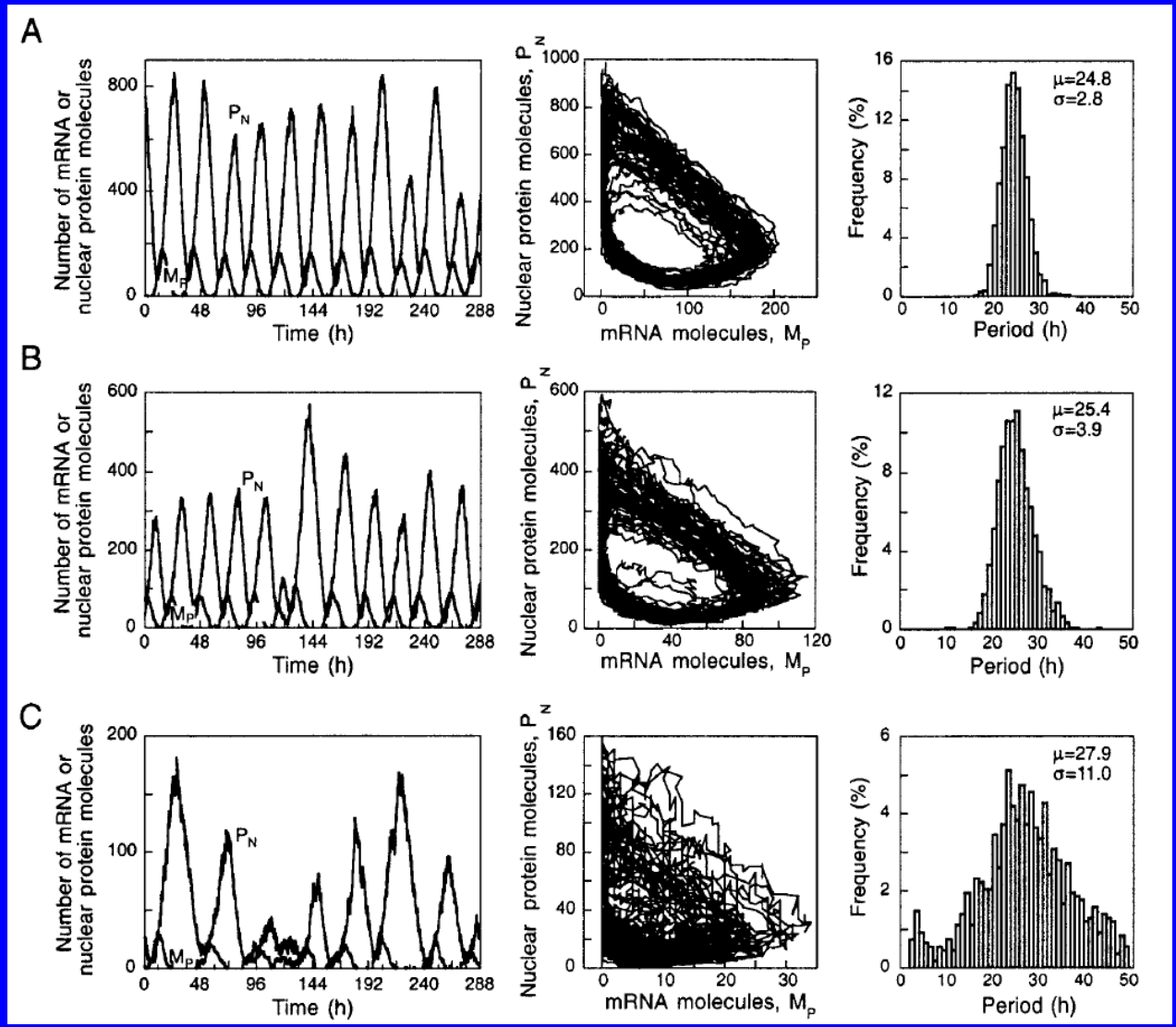
Circadian oscillations in the deterministic and stochastic case.

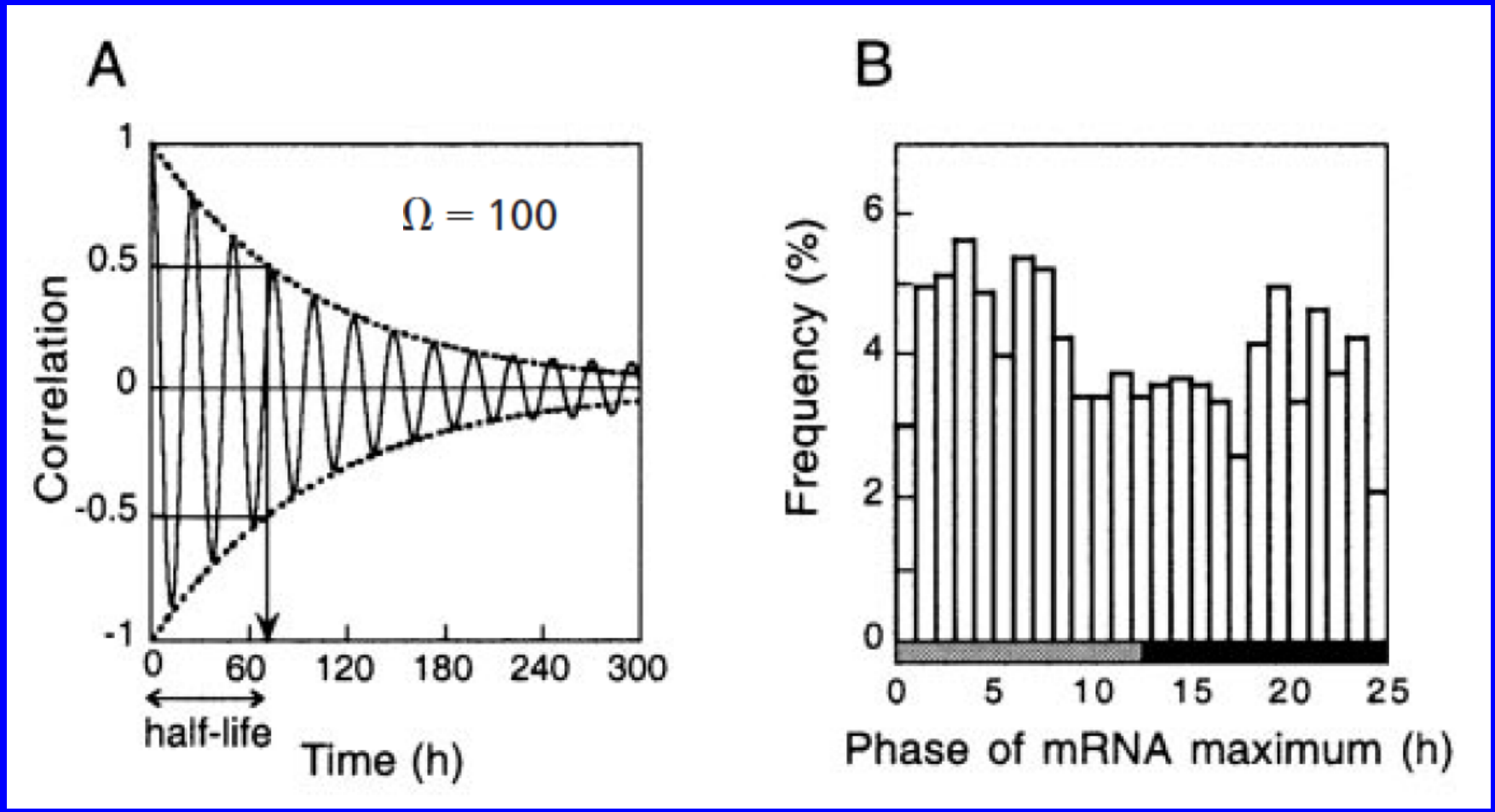
Effect of number of molecules on the robustness of circadian oscillations

$\Omega = 100$

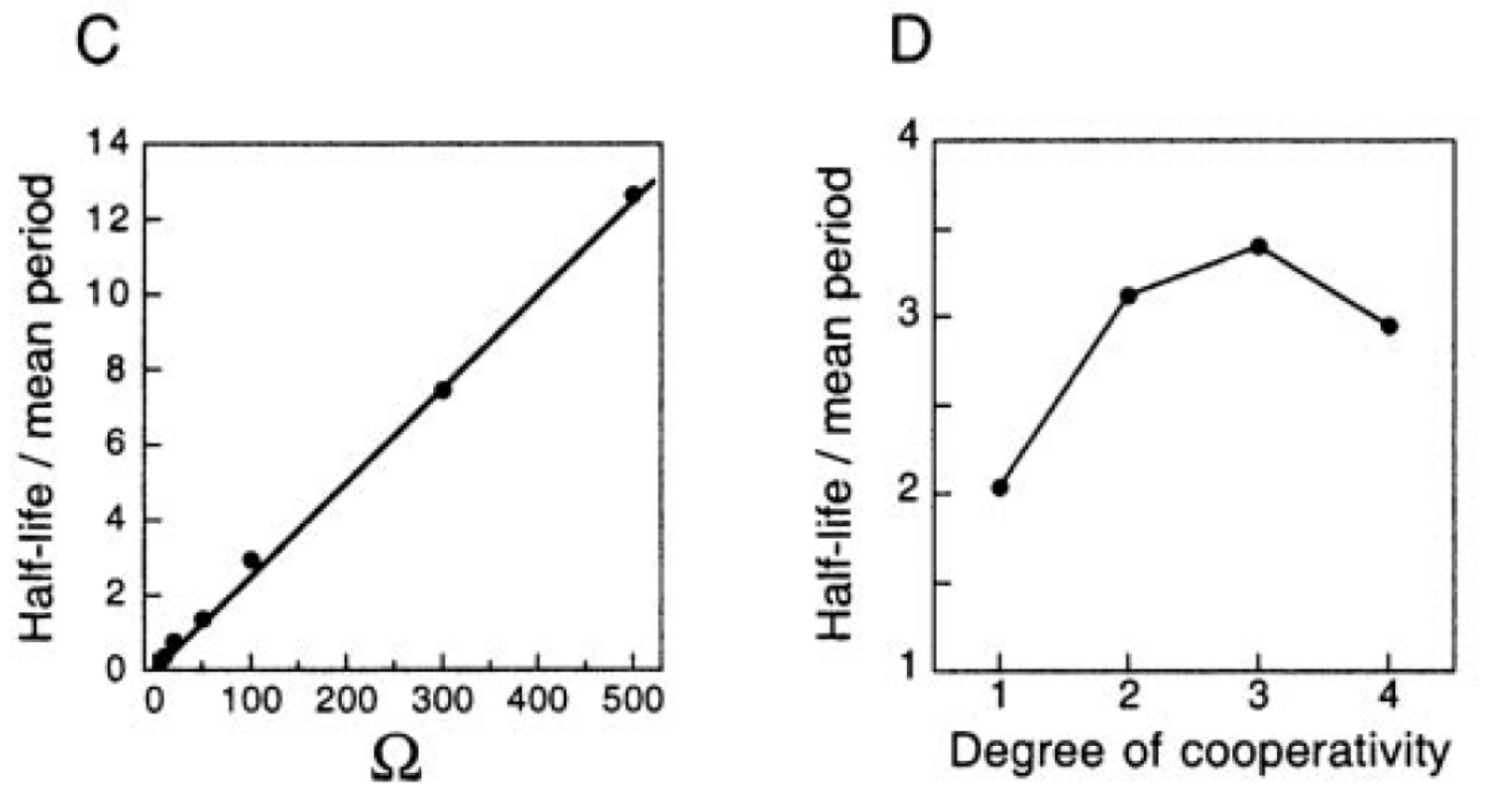
$\Omega = 50$

$\Omega = 10$





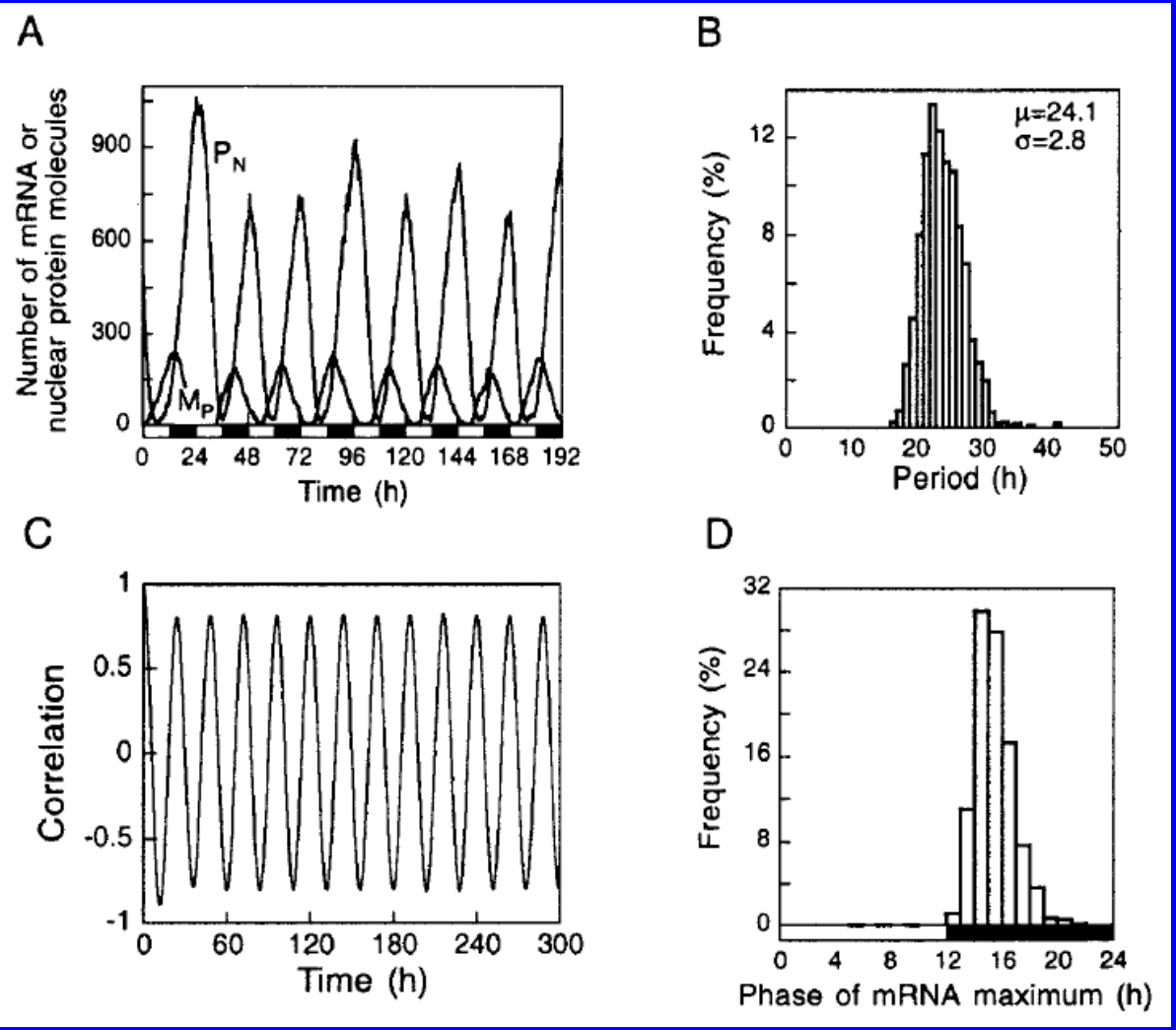
(*A*) Time evolution of the autocorrelation function; (B) Phase of maximum in mRNA in the presence of molecular noise.



(*C*) Half-life of autocorrelations increases in a linear manner with the parameter Ω. (D) Influence of the degree of cooperativity of repression on the robustness of circadian oscillations.

Entrainment by LD cycles in the presence of noise

$\Omega = 100$



Summary I

- We show that robust circadian oscillations can occur already with a limited number of mRNA and protein molecules, in the range of tens and hundreds, respectively.

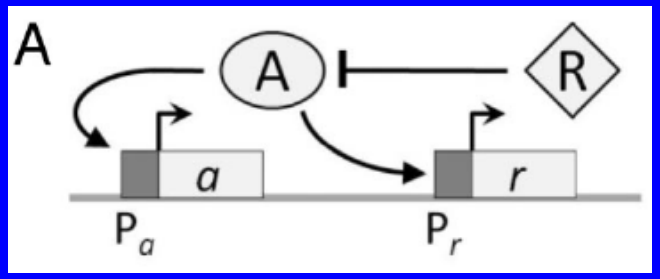
- Entrainment by light/dark cycles and cooperativity in repression enhance the robustness of circadian oscillations with respect to molecular noise.

2. A genetic timer through noise-induced stabilization of an unstable state

- Typically, noise causes perturbations that can **permit genetic circuits to escape stable states**, triggering, for example, phenotypic switching.
- In contrast, studies have shown that noise can surprisingly also **generate new states**, which exist solely in the presence of fluctuations.
- Here, we present a mechanism in which **noise intrinsic to a simple genetic circuit effectively stabilizes a deterministically unstable state**.

Turcotte, M., J. Garcia-Ojalvo, et al. (2008). PNAS **105**(41): 15732-15737.

Schematic diagram of the activator–repressor circuit



$$P_A^{const} \xrightarrow{k_1} P_A^{const} + mRNA_A$$

$$P_A \xrightarrow{f(A,k_2,K_a,n)} P_A + mRNA_A$$

$$P_R^{const} \xrightarrow{k_3} P_R^{const} + mRNA_R$$

$$P_R \xrightarrow{g(A,k_4,K_r,p)} P_R + mRNA_R$$

$$mRNA_A \xrightarrow{k_5} mRNA_A + A$$

$$mRNA_R \xrightarrow{k_6} mRNA_R + R$$

$$R + A \xrightarrow{k_7/\Omega} R$$

$$mRNA_A \xrightarrow{k_8} \varnothing$$

$$mRNA_R \xrightarrow{k_9} \varnothing$$

$$A \xrightarrow{k_{10}} \varnothing$$

$$R \xrightarrow{k_{11}} \varnothing$$

$$\Omega = VA = 1.66\mu m^3 \times 6.023 \cdot 10^{23} molec/mol = 1 \ molec/nM$$

$$f(A, k_2, K_a, n) = \frac{k_2 A^n}{K_a^n + A^n}, \qquad g(A, k_4, K_r, p) = \frac{k_4 A^p}{K_r^p + A^P}$$

$$\frac{da}{dt} = k_1 + \frac{k_2 A^n}{K_a^n + A^n} - k_8 a$$

$$\frac{dr}{dt} = k_3 + \frac{k_4 A^p}{K_r^p + A^p} - k_9 r$$

$$\frac{dA}{dt} = k_5 a - k_7 AR - k_{10} A$$

$$\frac{dR}{dt} = k_6 r - k_{11} R$$

$$\frac{dA}{dt} = \alpha_a + \frac{\beta_a A^n}{k_a^n + A^n} - \delta AR - \lambda_a A$$

$$\frac{dR}{dt} = \alpha_r + \frac{\beta_r A^p}{k_r^p + A^p} - \lambda_r R$$

$$\alpha_a = \frac{k_1 k_5}{k_8}, \quad \beta_a = \frac{k_2 k_5}{k_8}, \quad \alpha_r = \frac{k_3 k_6}{k_9}, \quad \beta_r = \frac{k_4 k_6}{k_9}$$

$$\delta = k_7, \quad \lambda_a = k_{10}, \quad \lambda_r = k_{11}$$

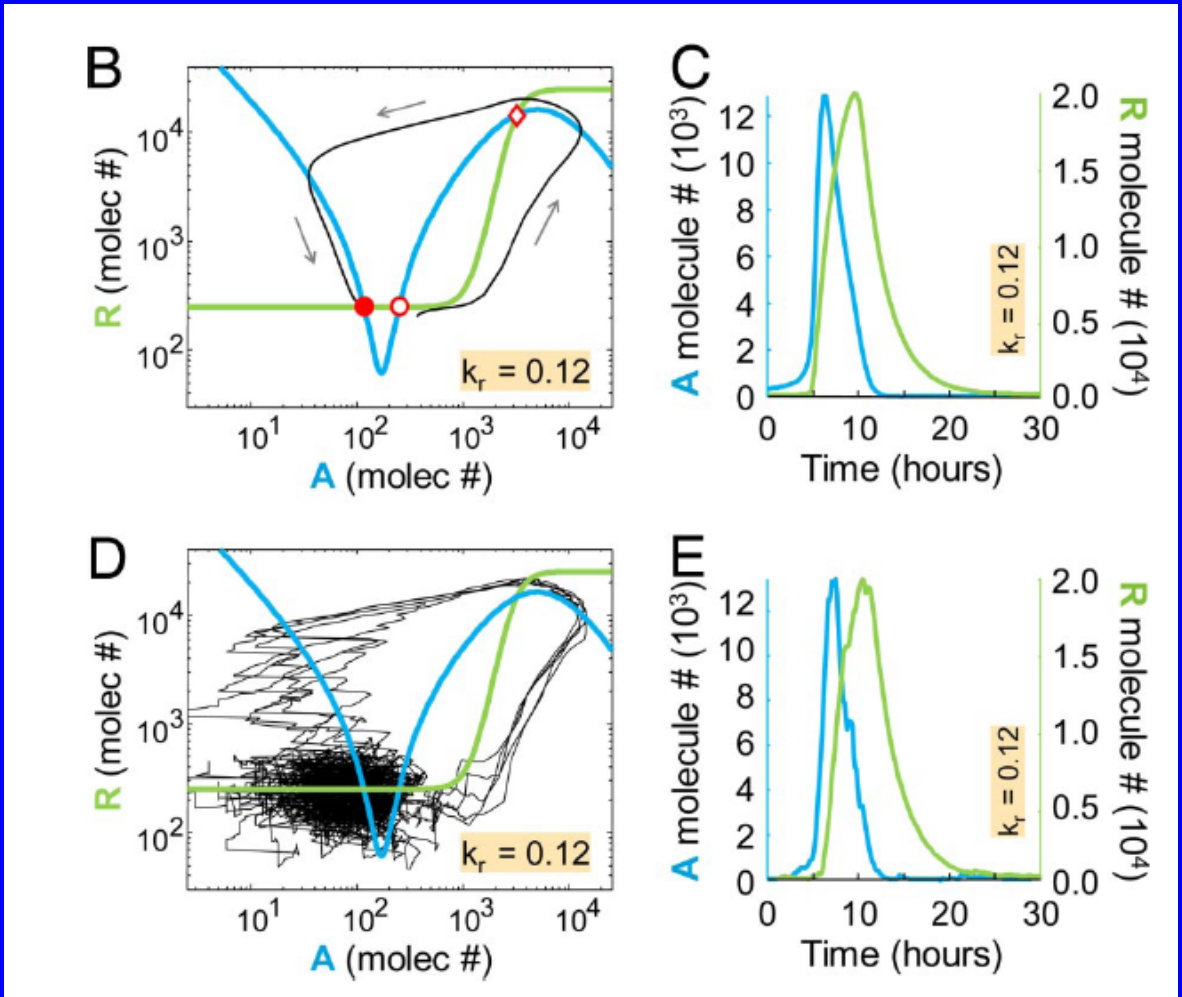


Fig.1: Continuous and discrete stochastic simulations of a simple activator–repressor circuit generate qualitatively identical excitable dynamics

Fig.2A: Enlarged view around the upper fixed point

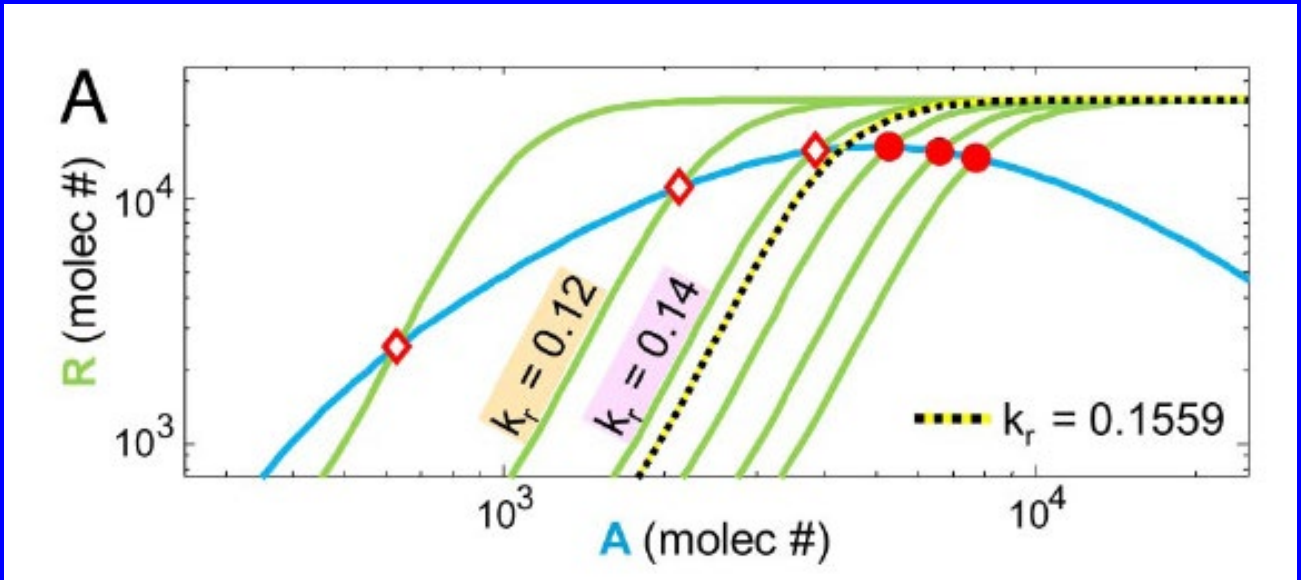


Fig.2：Near a bifurcation, noise induces qualitative differences in activator–repressor circuit dynamics.

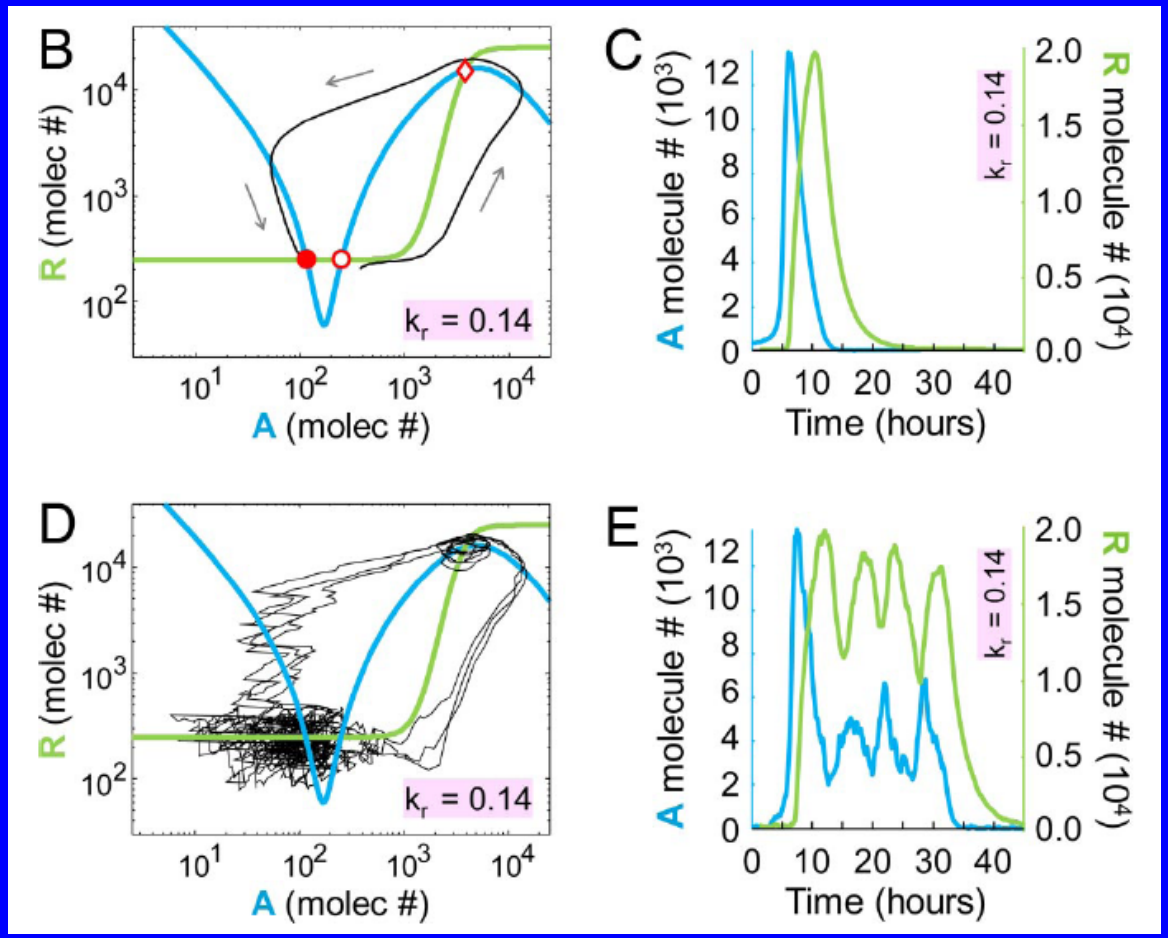
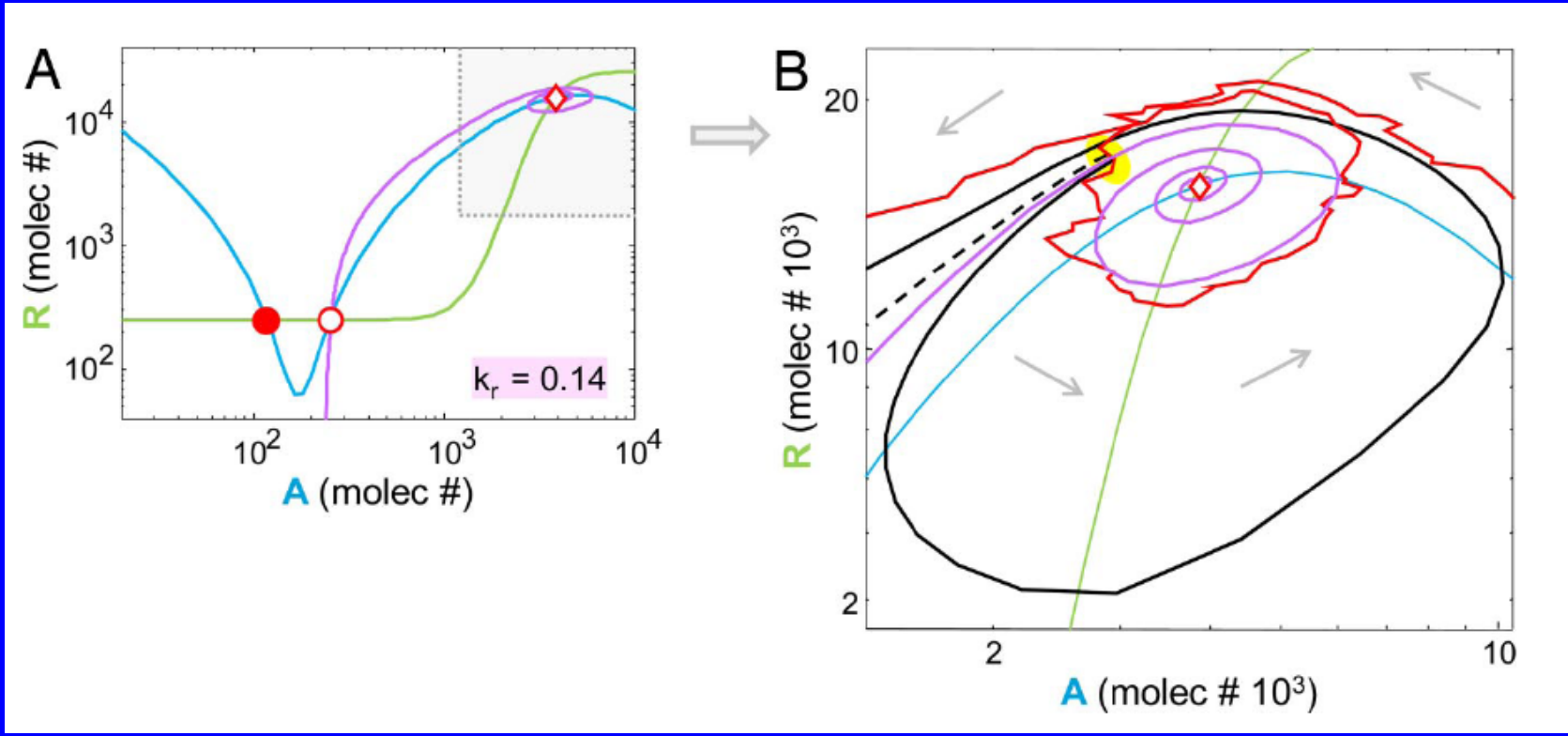


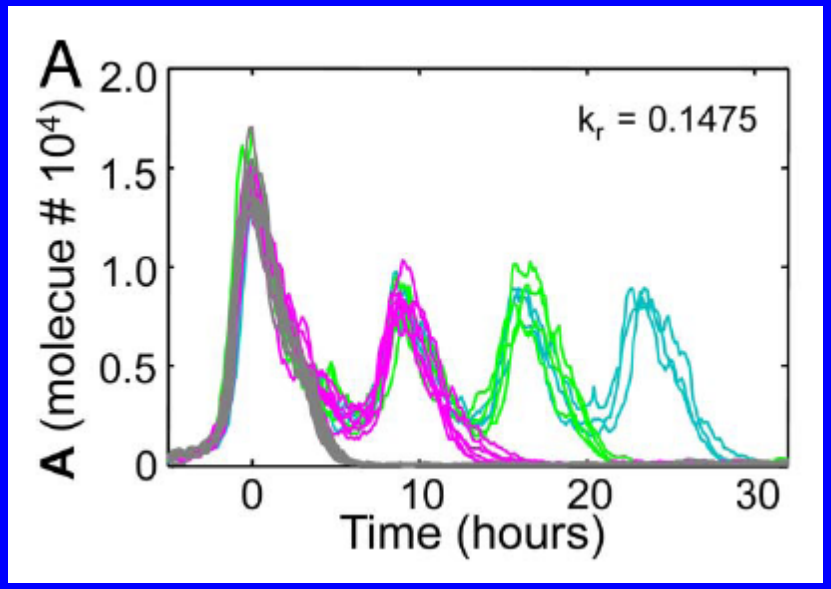
Fig.2: Near a bifurcation, noise induces qualitative differences in activator–repressor circuit dynamics.

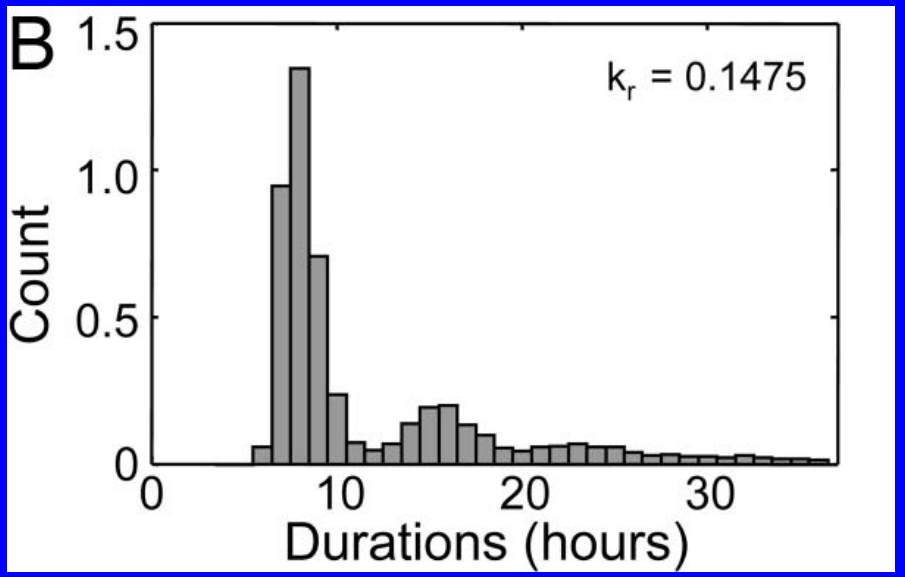
Noise effectively stabilizes a deterministically unstable fixed point



稳定流形是动力系统的不动点或周期轨附近当时间趋于正无穷时会趋于该轨的点的集合。

Noise-induced stabilization generates quantized durations of activator–repressor circuit dynamics

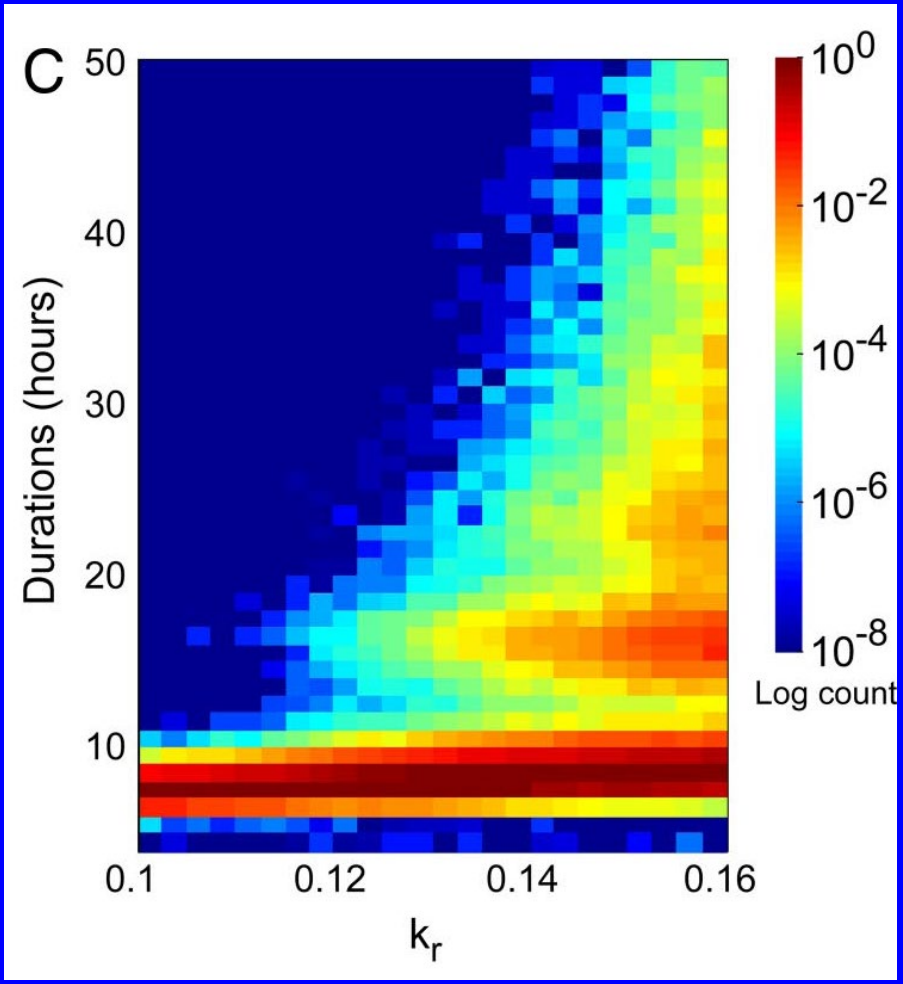




(*A*) Sample time traces aligned in time with respect to maximum of first high molecule number peak.

(B) Histogram of duration times in high-activity state obtained from 5,000 trajectories .

(*C*) Histograms of high-activity-state durations (as shown in
for indicated k_r values,



Summary II

- Near one such bifurcation, noise induces oscillations around an unstable spiral point and thus effectively stabilizes this unstable fixed point.

- Because of the periodicity of these oscillations, the lifetime of the noise-dependent stabilization exhibits a polymodal distribution with multiple, well defined, and regularly spaced peaks.

3. Enhancement of internal-noise coherence resonance by modulation of external noise in a circadian oscillator

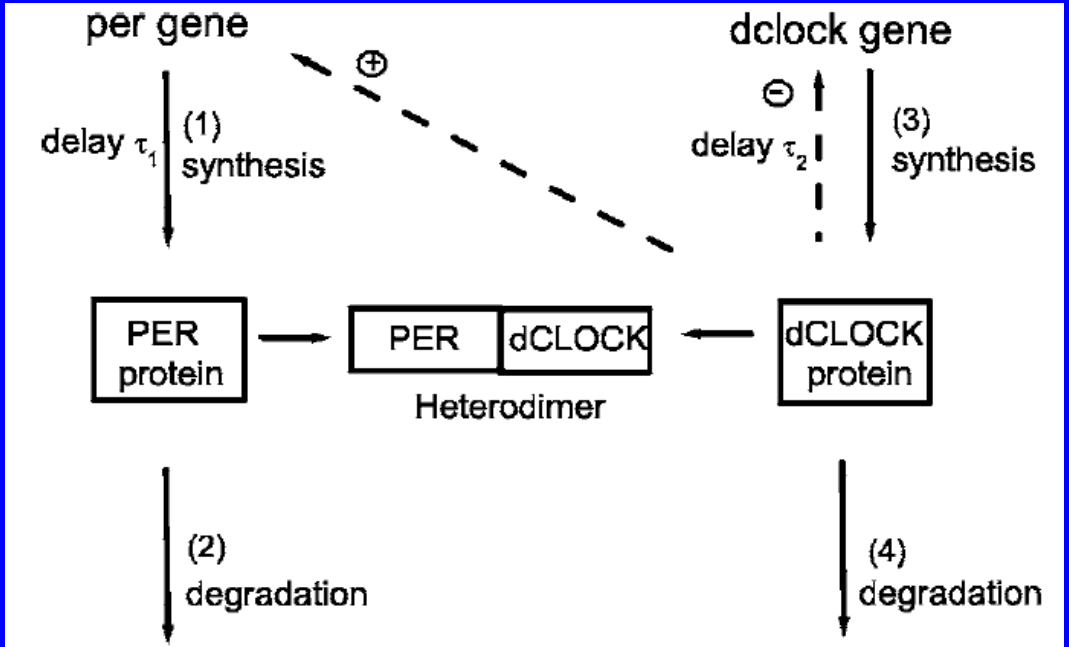


FIG. 1. Schematic of model. The *dCLOCK* protein activates the synthesis of *PER*. *PER* represses its own synthesis indirectly, by binding and inactivated *dCLOCK*. *dCLOCK* also represses its own synthesis. There are four elementary biochemical reaction processes marked with (1)–(4) respectively.

Yi M et al. Phys. Rev. E, 74: 041923 (2006)

$$L_{\text{free}} = (L - P)$$

$$\frac{dP(t)}{dt} = [v_{sp}R_{sp} - k_{dp}P(t)] + \frac{1}{\sqrt{V}}[\sqrt{v_{sp}R_{sp}}\xi_1(t) - \sqrt{k_{dp}P(t)}\xi_2(t)],$$

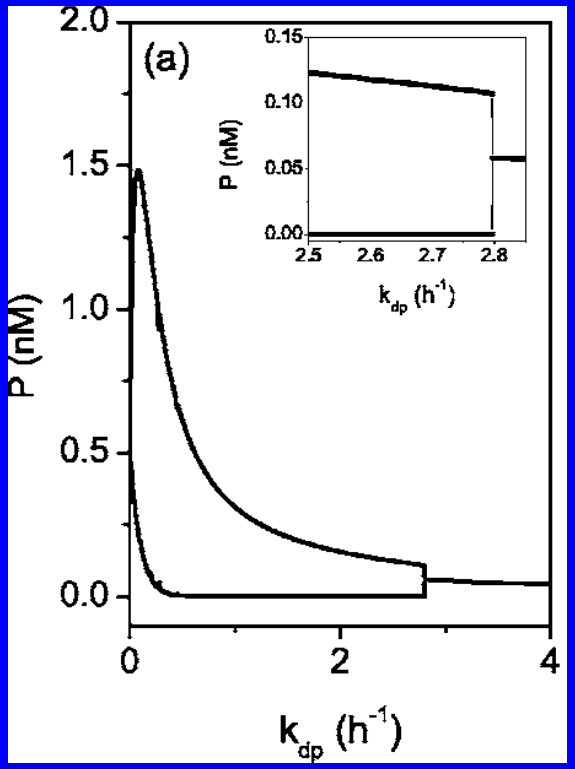
$$R_{sp} = \frac{L_{\text{free}}(t - \tau_1)}{K_1 + L_{\text{free}}(t - \tau_1)},$$

$$R_{sc} = \frac{K_2}{K_2 + L_{\text{free}}(t - \tau_2)},$$

$$\frac{dL(t)}{dt} = [v_{sc}R_{sc} - k_{dc}L(t)] + \frac{1}{\sqrt{V}}[\sqrt{v_{sc}R_{sc}}\xi_3(t) - \sqrt{k_{dc}L(t)}\xi_4(t)]$$

Transition processes	Description	Transition rates
(1) $p \to p+1$	The synthesis of *PER* activated directly by *dCLOCK* and repressed indirectly by itself	$a_1 = Vv_{sp}\frac{L_{\text{free}}(t-\tau_1)}{K_1+L_{\text{free}}(t-\tau_1)}$
(2) $p \to p-1$	The degradation of *PER*	$a_2 = Vk_{dp}P(t)$
(3) $l \to l+1$	The synthesis of *dCLOCK* activated indirectly by *PER* and represented directly by itself	$a_3 = Vv_{sc}\frac{K_2}{K_2+L_{\text{free}}(t-\tau_2)}$
(4) $l \to l-1$	The degradation of *dCLOCK*	$a_4 = Vk_{dc}L(t)$

$$k_{dp}^{0} = 2.85\ \mathrm{h}^{-1}$$



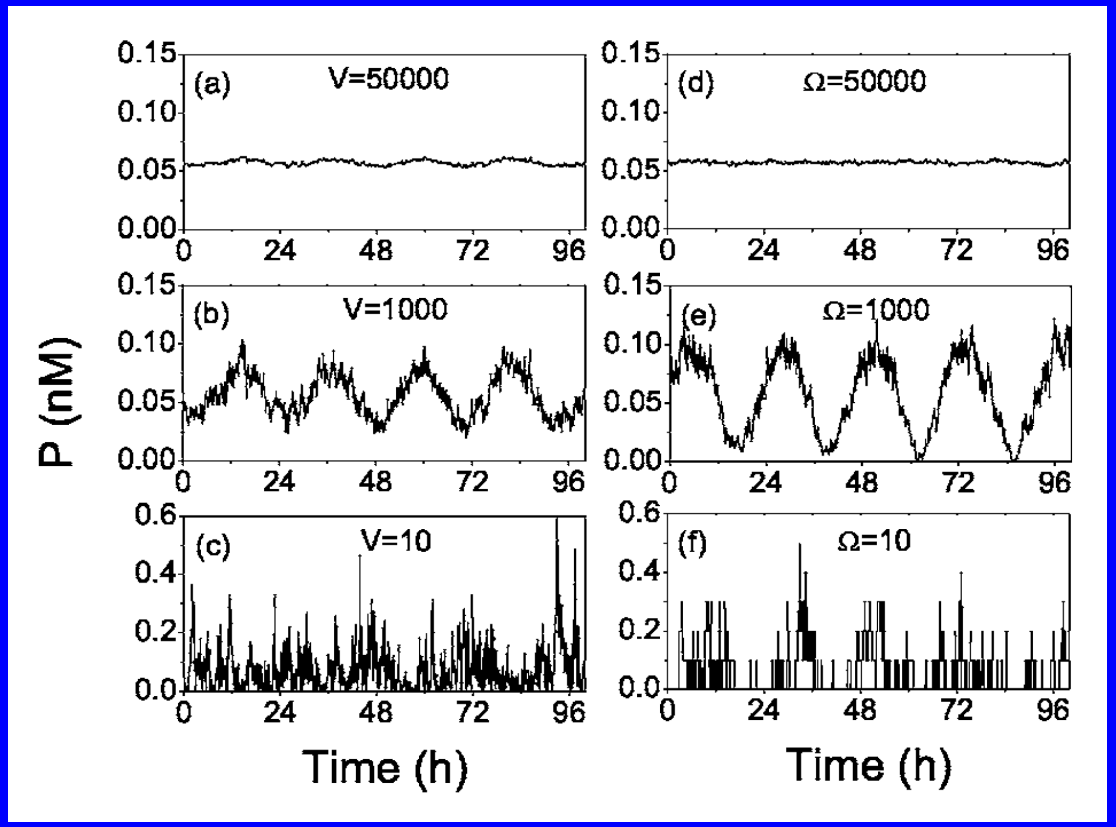


FIG. 2. Time series of *PER* concentration [(a)–(c)] via CLE and [(d)–(f)] from fixed time-step algorithm for different system size: from top to bottom $V=\Omega=5000$, 1000, and 10.

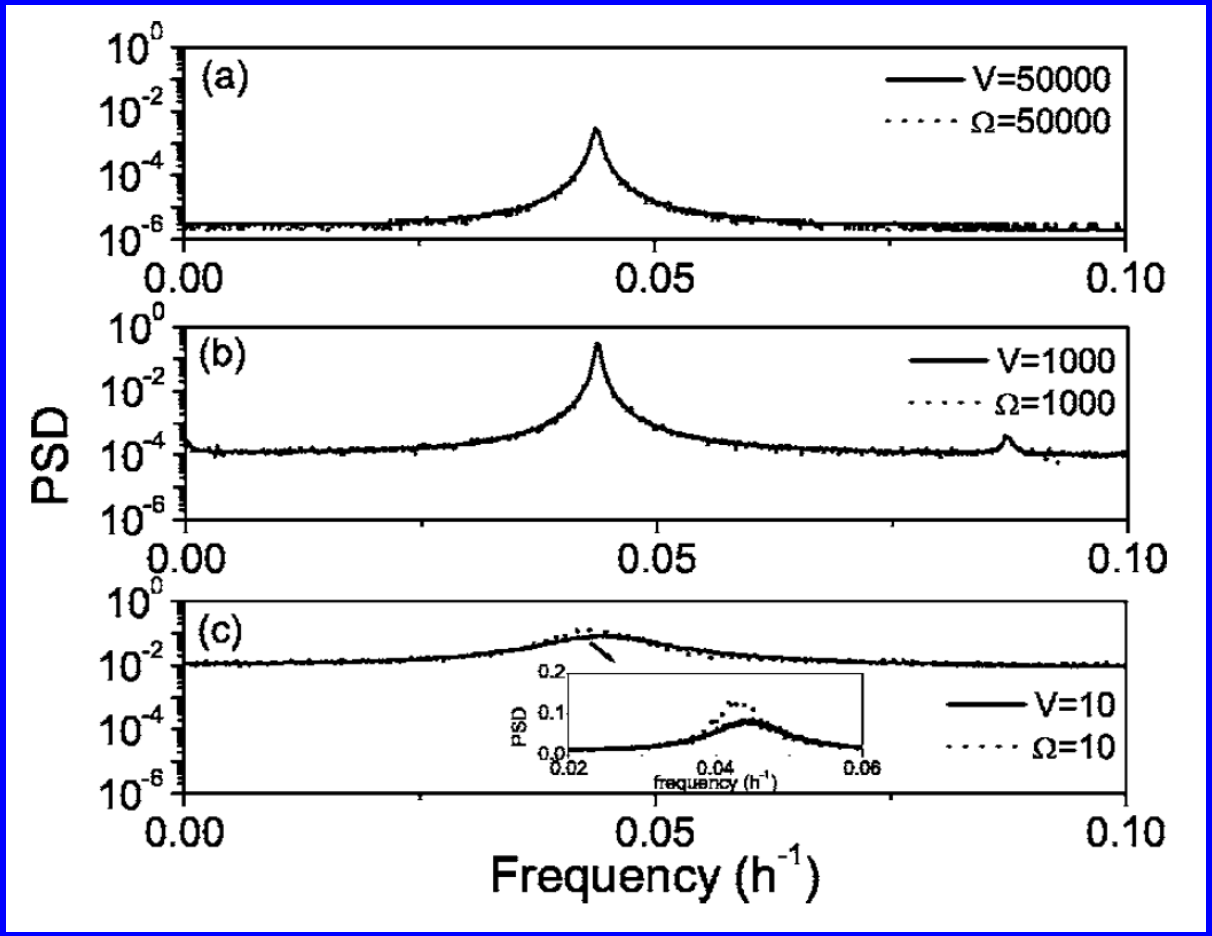
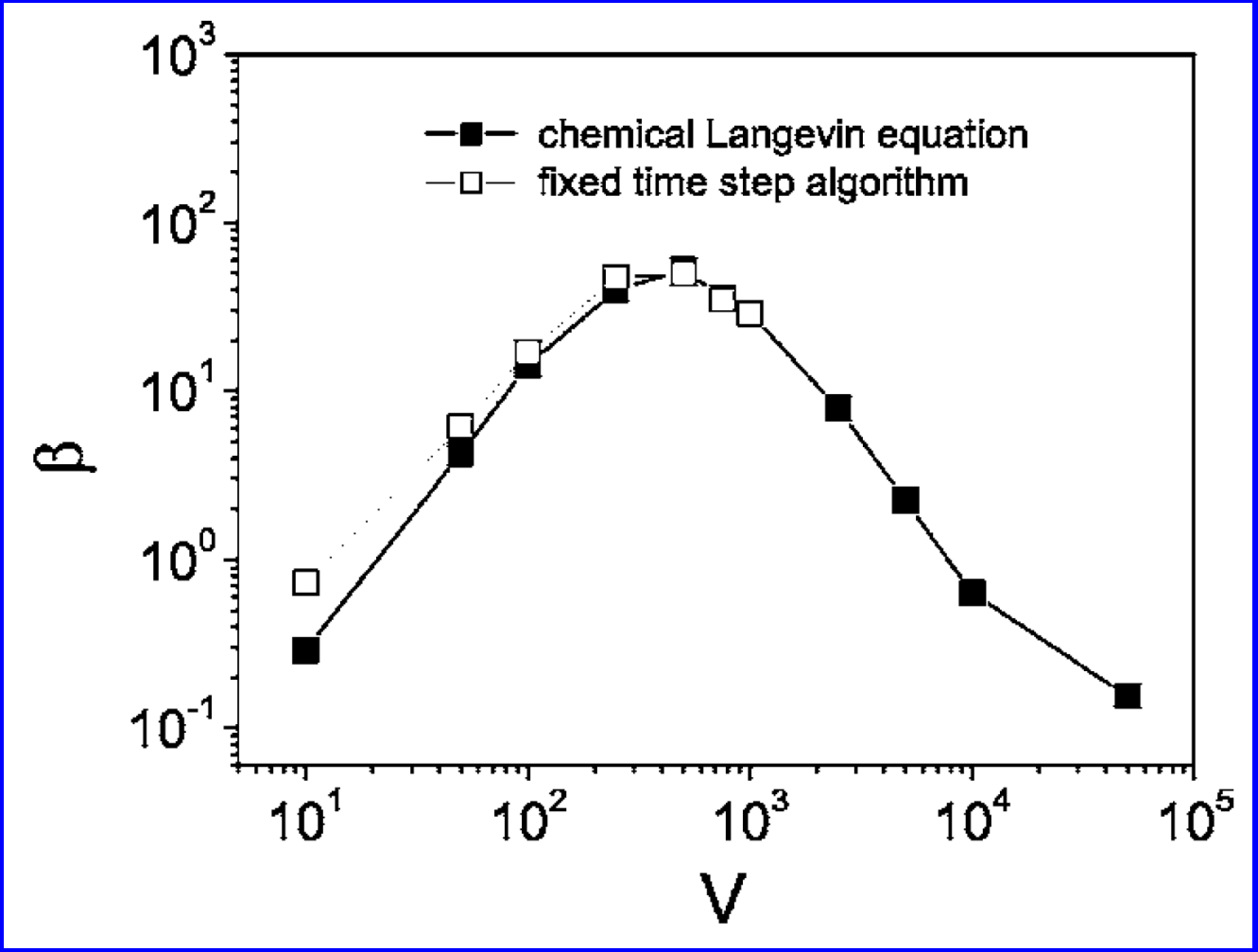


FIG. 3. The power spectral density [(a)–(c)] of *PER* concentration for different system size: from top to bottom $V=\Omega=5000$, 1000, and 10. Solid lines: data from CLE; dotted lines: data from fixed time step algorithm.

Dependence of SNR on noise intensity

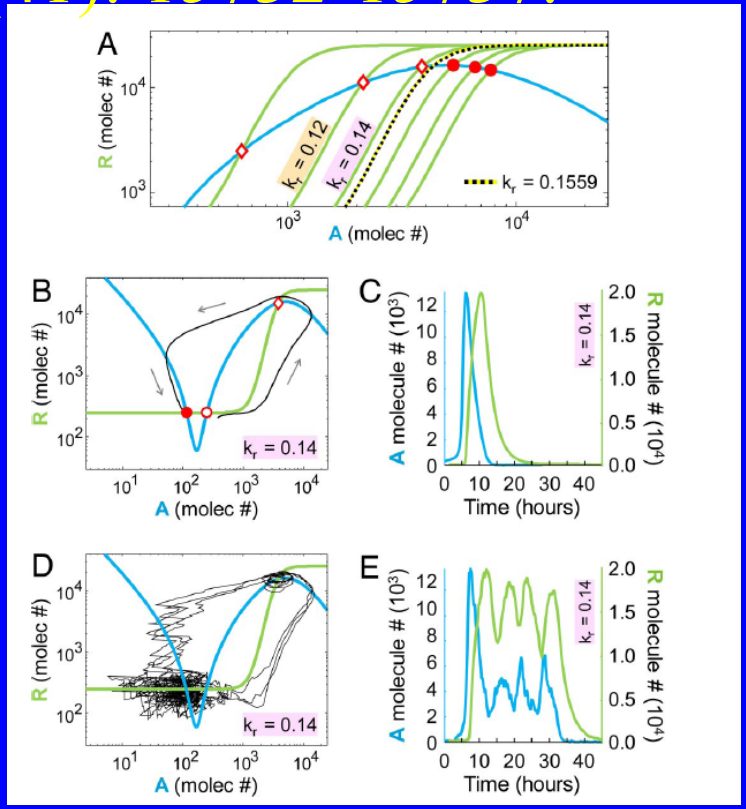


Assignment 10

Reproducing Fig.2 and plot the bifurcation diagram of R vs k_r in the following literature: Turcotte, M., J. Garcia-Ojalvo, et al. (2008). PNAS 105(41): 15732-15737.

$$\frac{dA}{dt} = \alpha_a + \frac{\beta_a A^n}{k_a^n + A^n} - \delta A R - \lambda_a A$$

$$\frac{dR}{dt} = \alpha_r + \frac{\beta_r A^p}{k_r^p + A^p} - \lambda_r R$$



The Michaelis constants are $K_a = k_a\Gamma$ and $K_r = k_r\Gamma$, where $\Gamma = 2.5{\cdot}10^4$ molecules