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Internal Noise Coherent Resonance for Mesoscopic Chemical Oscillations: A Fundamental Study

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The effect of internal noise for a mesoscopic chemical oscillator is studied analytically in a parameter region outside, but close to, the supercritical Hopf bifurcation. By normal form calculation and a stochastic averaging procedure, we obtain stochastic differential equations for the oscillation amplitude r *and phase* θ *that is solvable. Noise-induced oscillation and internal noise coherent resonance, which has been observed in many numerical experiments, are reproduced well by the theory.*

Very recently, the effects of internal molecular noise in small-scale chemical reaction systems, where the number of reactant molecules can be low, has gained much attention.[1,2] Examples of such mesoscopic chemical systems include gene expression,[3] circadian oscillation,[4–6]ion-channel gating,[7] calcium signaling[8] taking place in subcellular spaces, or catalytic reactions on the surface of nanoparticles[9,10] or field-emit tips,[11,12] to name just a few. While most of the studies so far have focused on the design of reaction mechanisms or regulatory architectures to be robust against the unavoidable molecular noise, another interesting phenomenon, where internal noise may also be exploited to play a constructive role, is of particular interest. Specifically, for mesoscopic chemical reactions showing oscillatory behavior, it was reported that internal noise can induce oscillation, even in a parameter region where only the steady-state can be observed in a corresponding macroscopic system. In addition, the signal-to-noise ratio (SNR) of the noise induced oscillation (NIO) undergoes a maximum when the noise intensity is varied, indicating the occurrence of internal noise coherent resonance (INCR).[13–22] Since the internal noise intensity is often inversely proportional to some kind of system size, such behavior has also been named "system-size resonance". For instance, Hänggi and co-workers and Shuai and Jung reported that ion-channel clusters of an optimal size were the most favorable for intracellular calcium signaling;[13–17] and in a few previous studies, we have also found such behavior for calcium signaling,[18] circadian oscillation,[19] surface catalytic reactions,[20,21] and the Brusselator system.[22]

Herein, we give a fundamental understanding of the NIO and INCR. Since they all happen close to the deterministic Hopf bifurcation point, we believe that some universal properties of the Hopf bifurcation must be relevant. From the theory of dynamical systems, we know that, near the Hopf bifurcation, the system's dynamics can be described by a normal form involving the evolution of a complex amplitude Z in the center manifold.[23] Starting from chemical Langevin equations (CLE), which clearly combine the deterministic dynamics and contributions from internal noises, and by performing a normal form calculation and stochastic averaging procedure, we obtain stochastic differential equations for the oscillation amplitude r and phase θ that is solvable. The analytical results show rather good agreement with the numerical results, hence the NIO and INCR have been well explained. Our analysis also provides a starting point for the investigation of internal molecular noise near the Hopf bifurcation.

To account for the internal molecular noise in mesoscopic chemical reactions, one can basically view the system as a Markovian stochastic birth–death process and write down a chemical master equation governing the evolution of the probability of having a given number of reactant molecules.[24] Very recently, Gillespie argued that a system's temporal behavior may also be described by a chemical Langevin equation, given that a macroinfinitesimal timescale exists.[25] Generally, if the system size V is not too small, such a condition is expected to be fulfilled and the CLE works, at least in a qualitative manner. Also, such a CLE is consistent with the Fokker–Planck equation associated with the master equation.[25] In our previous studies,[18–22] it was shown that CLE was in good qualitative agreement with other exact simulation algorithms, making it a convenient method for studying the role of internal noise. One more benefit of the CLE is that it clearly relates to the system's deterministic dynamics, and it is deservedly a suitable starting point for analytical treatments, especially when bifurcation happens.

For simplicity, but without losing generality, we consider the conceptual Brusselator model involving two species X_1 and X_2 and $M=4$ reaction channels. The reaction steps are $A \rightarrow X_1$, $B + X_1 \rightarrow X_2$, $X_1 \rightarrow C$, $2X_1 + X_2 \rightarrow 3X_1$ where species A and B are kept at constant concentrations such that the system is out of equilibrium. For certain choices of parameters, the rates are $\mathbf{w}_{j=1,\ldots,4} = (A, BX_1, X_1, X_1^2X_2)$. The CLE is given by Equation (1):[25]

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$$dX_\alpha = F_\alpha(\mathbf{X})dt + \frac{1}{\sqrt{V}}\sum_{j=1}^{M} v_{j\alpha}\sqrt{w_j}dW_j(t) \quad (\alpha = 1,2) \tag{1}$$

where we also use X_1 and X_2 to stand for the concentrations, V is the system size (volume), $F_\alpha(X) = \sum_{j=1}^{M} v_{j\alpha} w_j(X)$, $\nu_{j1} = (1,-1,-1,1)$ and $\nu_{j2} = (0,1,0,-1)$ are the stoichiometric change of species X_1 and X_2, respectively; $dW_{j=1,\ldots,M}(t)$ are M independent Wiener processes associated with the M reaction channels, with $\langle dW_j(t)\rangle = 0$ and $\langle dW_j(t)dW_{j'}(t')\rangle = \delta_{jj'}\delta(t-t')dt$ and t it the time. In the macroscopic limit $V\to\infty$, the internal noise terms can be ignored, resulting in the deterministic dynamics $dX_\alpha/dt = F_\alpha(\boldsymbol{X})$, which has a supercritical Hopf bifurcation at $B = B_c = A^2+1$.

The calculation of the normal form for the Brusselator model is standard, but one should pay attention to the internal noise terms. Since the CLE, Equation (1), is interpreted in Ito manner, one should first transform it into a Stratonovich form, which allows for normal calculus during variable transformation [Eq. (2)]:[26]

$$dX_\alpha = F'_\alpha(X)dt + \frac{1}{\sqrt{V}}\sum_{j=1}^{M} v_{j\alpha}\sqrt{w_j}\circ dW_j(t) \quad (\alpha = 1,2) \tag{2}$$

where $\circ$ stands for Stratonovich interpretation, $F'_\alpha(X) = F_\alpha(X) - \sum_j v_{j\alpha}\eta_j(X)$, and $\eta_j(X) = \frac{1}{4V}\sum_\beta \frac{\partial w_j}{\partial X_\beta}$ results from the transformation from the Ito to Stratonovich calculus. Note that $F'(\boldsymbol{X})$ has equilibrium points $\mathbf{X}_S$ and a Hopf bifurcation value B'_c slightly different from that of $F(\boldsymbol{X})$, but the discrepancies are only of the order of $1/V$. For $B \simeq B'_c$, the Jacobi matrix $\mathbf{J}_{\alpha\beta} = (\partial_\alpha F'_\beta)_{(\mathbf{X}_S)}$ has two conjugate eigenvalues $\mu \pm i\omega_0$, with eigenvectors $(1, a \pm ib)$. By variable transformation [Eq. (3)]:

$$x = X_1 - X_{1S},\ y = [(X_2 - X_{2S}) - a(X_1 - X_{1S})]/b, Z = x + iy = re^{i\theta} \tag{3}$$

Equations (4a) and (4b) are obtained:

$$dr = (\mu r + C_r r^3)dt + \frac{1}{\sqrt{V}}\sum_j \chi_{rj}\circ dW_j \tag{4a}$$

$$d\theta = (\omega_0 + C_i r^2)dt + \frac{1}{\sqrt{V}}\sum_j \chi_{\theta j}\circ dW_j \tag{4b}$$

where C_r and C_i are constants associated with the nonlinear deterministic terms near the Hopf bifurcation; $\chi_{rj} = (\tilde{\nu}_{j1}\cos\theta + \tilde{\nu}_{j2}\sin\theta)\sqrt{w_j}$ and $\chi_{\theta j} = (-\tilde{\nu}_{j1}\sin\theta + \tilde{\nu}_{j2}\cos\theta)\sqrt{w_j}/r$; $\tilde{\nu}_{j1}$ and $\tilde{\nu}_{j2}$ are linearly transformed from ν_{j1} and ν_{j2} via $\tilde{\nu}_{j1} = \nu_{j1}$ and $\tilde{\nu}_{j2} = (\nu_{j2} - a\nu_{j1})/b$.

The deterministic parts in Equations (4a) and (4b) are familiar to us, where the two variables r and θ are separated and there exists a stable limit cycle $r_0 = \sqrt{\mu/(-C_r)}$ only in the supercritical region $\mu > 0$. However, when the internal noise is considered, r and θ are strongly coupled to each other through $\sqrt{w_j}$ in the internal noise terms, which may lead to interesting new dynamics. Unfortunately, the complicated form of the noise terms renders the direct analysis of Equations (4a) and (4b) a rather difficult task. Therefore, we turn to the "stochastic averaging" procedure, which has been successfully used in studying stochastic nonlinear oscillators, such as the Duffing system.[27] The basic idea of stochastic averaging is to approximate the systems in Equations (4a) and (4b) as Markov processes in the long-time limit. This is possible for $|\mu| \ll 1$ and $V \gg 1$. Consequently, one can approximate Equations (4a) and (4b) with Ito stochastic differentials, Equations (5a) and (5b):

$$dr = \left[\mu r + C_r r^3 + \frac{K(r)}{2Vr}\right]dt + \frac{\varepsilon_r}{\sqrt{V}}dW_r \tag{5a}$$

$$d\theta = \left[\omega_0 + C_i r^2 + \frac{K(\theta)}{2V}\right]dt + \frac{\varepsilon_\theta}{\sqrt{V}r}dW_\theta \tag{5b}$$

where $K(r)/r = \sum_j \int_0^{2\pi} (\chi_{rj}\partial_r\chi_{rj} + \chi_{\theta j}\partial_\theta\chi_{rj})d\theta/2\pi$, $K(\theta) = \sum_j \int_0^{2\pi} (\chi_{rj}\partial_r\chi_{\theta j} + \chi_{\theta j}\partial_\theta\chi_{\theta j})d\theta/2\pi$ results from the coupling between r and θ, $\varepsilon_r^2 = \sum_j \int_0^{2\pi} \chi_{rj}^2 d\theta/2\pi$, $\varepsilon_\theta^2/r^2 = \sum_j \int_0^{2\pi} \chi_{\theta j}^2 d\theta/2\pi$ are the average noise intensities associated with the approximated Markov process; dW_r and dW_θ are two "new", independent Wiener processes. Writing w_j in the form $w_j = \sum_{k+l=0}^{3} w_j^{(kl)}(r\cos\theta)^k(r\sin\theta)^l$, we find that $K(\theta)$ is exactly zero, and only that coefficients with even $k+l$ have non-zero contributions to $K(r)$, ε_r^2, and ε_θ^2. They all have the form $\varepsilon^2 + \gamma r^2$, where $\varepsilon^2 = \sum_j (\tilde{\nu}_{j1}^2 + \tilde{\nu}_{j2}^2)w_j^{(00)}/2$. γ is a constant determined by the coefficients $w_j^{k+l=2}$. For a small internal noise level, $r^2 \ll 1$ is a good approximation, it is feasible to neglect the contributions from $w_j^{k+l=2}$. Hence, we finally reach rather simplified forms, such as $K(r) = \varepsilon_r^2 = \varepsilon_\theta^2 = \varepsilon^2$.

A key point in Equation (5a) is that a new deterministic term $K(r)/2Vr \equiv \varepsilon^2/2Vr$ appears. Even in the parameter region subthreshold to the Hopf bifurcation, that is, $\mu < 0$, one still can find non-zero solutions for $\mu r + C_r r^3 + \varepsilon^2/2Vr = 0$, which is $r_s = \left[\left(\sqrt{\mu^2 - 2C_r\varepsilon^2/V} + \mu\right)/(-2C_r)\right]^{1/2}$. Therefore, we already get an NIO with non-zero amplitude, most probably r_s. One notes that a non-zero $w_j^{(00)}$ is necessary for the occurrence of NIO, which is related to the non-zero equilibrium values X_{1S} and X_{2S}, a common feature of chemical reactions. That is, although non-zero steady-state values are not necessary for deterministic oscillation, they play a key role in the noisy dynamics. Though we chose the Brusselator as our example, one can see that the above analysis is not system-specific, and thus NIO is a universal phenomenon for chemical reactions staying outside, but close to, the supercritical Hopf bifurcation.

In previous numerical studies, the performance of the NIO has often been characterized by the effective SNR, which is defined as the peak height in the power spectrum divided by the peak width.[22] Since the variable r is fully separated from θ in Equations (5a) and (5b), an analytical expression for the SNR is available. The Fokker–Planck equation associated with Equation (5a) is given by Equation (6):

$$\partial\rho(r,t) = -\partial_r\left[\left(\mu r + C_r r^3 + \frac{\varepsilon^2}{2Vr}\right)\rho\right] + \frac{\varepsilon^2}{2V}\partial_r^2\rho \tag{6}$$

and the stationary probability distribution function (PDF) of r is

given by Equation (7):

$$\rho_s(r) = C_0 r \exp\left(\frac{2\mu r^2 + C_r r^4}{2(\varepsilon^2/V))}\right) \tag{7}$$

where C_0 is a normalization constant. The PDF has a maximum at $r=r_s$, hence in the limit $t\to\infty$, the system will most probably stay around this noise-induced limit cycle. Writing $r(t)=r_s+\delta_r(t)$, we have $d\delta_r=-\lambda_1\delta_r dt+O(\delta_r^2 dt)+\sqrt{\varepsilon^2/V}dW_r(t)$ leading to $\lim_{t\to\infty}\langle\delta_r(t)\rangle=0$, $\lim_{t\to\infty}\langle\delta_r(t)\delta_r(t+\tau)\rangle\simeq\varepsilon^2 e^{-\lambda_1\tau}/2\lambda_1 V$, where $\lambda_1=2\sqrt{\mu^2-2C_r\varepsilon^2/V}$. These give the approximated correlation function of $r(t)$ as $\lim_{t\to\infty}\langle r(t)r(t+\tau)\rangle = r_s^2+\varepsilon^2 e^{-\lambda_1\tau}/2\lambda_1 V$, where τ is the time lag. After a sufficiently long time, $\rho(r,t)$ will reach the stationary distribution. Approximately, we may then replace r^2 and r^{-1} in Equation (5b) by their stationary mean values $\langle r^2\rangle_s$ and $\langle r^{-1}\rangle_s$ respectively. θ is then Gaussian distributed with a mean value $\langle\theta(t)\rangle=(\omega_0+C_i\langle r^2\rangle_s)t=\omega_1 t$ and variance $\langle\theta(t)^2\rangle-\langle\theta(t)\rangle^2=\varepsilon^2\langle r^{-1}\rangle_s^2 t/2V\equiv 2\lambda_2 t$. Using $\langle e^{j\theta}\rangle = e^{j\langle\theta\rangle}e^{-\left[\langle\theta^2\rangle-\langle\theta\rangle^2\right]/2}$,[26] we obtain Equation (8):

$$\lim_{t\to\infty}\langle\cos\theta(t)\cos\theta(t+\tau)\rangle = \frac{1}{2}\cos(\omega_1\tau)\exp(-\lambda_2\tau) \tag{8}$$

Now the autocorrelation function and corresponding power spectrum of the state variable $x=X_1-X_{1S}=r\cos\theta$ is calculated as Equations (9a) and (9b):

$$\begin{aligned} C(\tau) &= \lim_{t\to\infty}\langle x(t)x(t+\tau)\rangle \\ &\cong \frac{1}{2}\left(r_s^2+\frac{\varepsilon^2 e^{-\lambda_1 t}}{2\lambda_1 V}\right)\cos(\omega_1\tau)\exp(-\lambda_2\tau) \end{aligned} \tag{9a}$$

$$\begin{aligned} \mathrm{PSD}(\omega) &= 2\int_0^\infty C(\tau)e^{-i\omega\tau}d\tau \\ &= \left[\frac{r_s^2\lambda_2}{\lambda_2^2+(\omega-\omega_1)^2}+\frac{(\lambda_1+\lambda_2)\varepsilon^2/2\lambda_1 V}{(\lambda_1+\lambda_2)^2+(\omega-\omega_1)^2}\right] \end{aligned} \tag{9b}$$

Note that in Equation (9b) we have only kept the branch of positive ω near the resonance frequency ω_1.

By numerical calculations of Equation (9), the dependence of the PSD on the noise intensity can be readily obtained. In addition, it can be shown that the second term in the bracket of Equation (9b) is much smaller than the first one and can be neglected. Therefore, as a reasonable approximation, the peak locates at $\omega=\omega_1$, and the peak height, half width, and the effective SNR are given by Equations (10a)–(10c):

$$H = r_s^2/\lambda_2 \cong 2r_s^4 V/\varepsilon^2 \tag{10a}$$

$$\Delta\omega = \lambda_2 \cong \varepsilon^2/2Vr_s^2 \tag{10b}$$

$$\mathrm{SNR} = H/\Delta\omega = 4r_s^6 V^2/\varepsilon^4 \tag{10c}$$

By using $\partial(\mathrm{SNR})/\partial V=0$, we find the optimal system size locates at $V_{\mathrm{opt}}=-4C_r/\varepsilon^2\mu^2$. Note μ comes from the linear part of the system's dynamic equation, C_r from the nonlinear parts, and ε^2 is related to the steady-state concentrations; μ is a universal parameter, while C_r and ε^2 are system-specific. For the Brusselator, the parameter values are $C_r\simeq-3/8$, $C_i\simeq 1/24$, $\mu\simeq(B-1-A^2)/2$, $\varepsilon^2\simeq 4$. Note that we use $\simeq$ because small values, of the order of $1/V$, resulting from the transformation from Equation (1) to (2), have been neglected.

To check the validity of the above analysis, we performed a numerical simulation of Equation (1) with a time step of 0.01. Time series $X_1(t)$ and $X_2(t)$ were used to calculate $r(t)$ and $\theta(t)$ via Equation (3) and $r(t)=\sqrt{x^2(t)+y^2(t)}$, $\cos\theta(t)=x(t)/r(t)$. The distribution of $r(t)$ is shown in Figure 1, where excellent agreement with Equation (7) is observed. The autocorrelation function (ACF) of $\cos\theta(t)$ was also calculated, as shown in Figure 2a. By fitting the peaks in the ACF, one can numerically

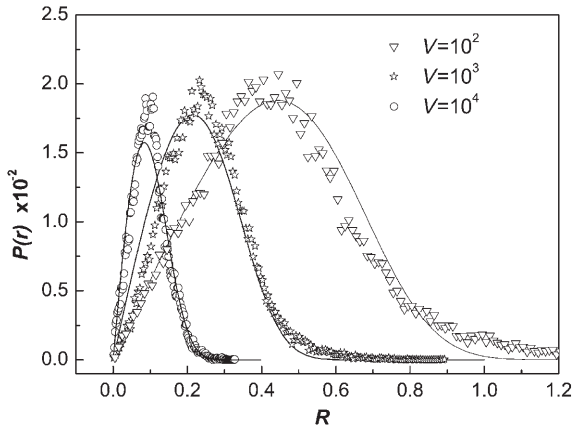

Figure 1. Stationary distribution of the radius of the noise-induced limit cycle obtained from numerical simulation (symbols) and Equation (7) (——). $\mu=-0.025$, $\log(V)=2,3,4$.

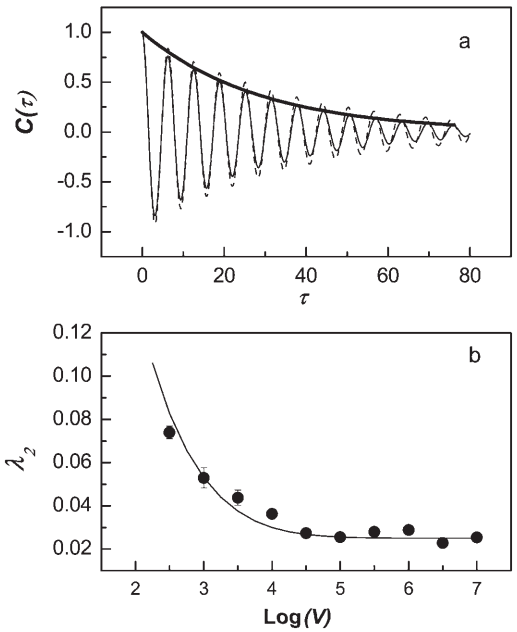

Figure 2. a) A typical autocorrelation function obtained from the theoretical formula, Equation (8) (– – –) and numerical calculations (——). —— is a fit using an exponential decay from which we can estimate the autocorrelation time. $\mu=0.025$, $V=10^4$. b) The reciprocal autocorrelation time λ_2 obtained from numerical fitting and the theoretical formula $\lambda_2=\varepsilon^2/2r_s^2V$. $\mu=-0.025$.

obtain the correlation time $\tau_0 = 1/\lambda_2$, which is drawn in Figure 2b. Again, the numerical results for $\theta(t)$ show rather good agreement with the analytical results. Please note, however, that quantitative comparison of the SNR values between the numerical results and the theory is difficult, because the accurate estimation of the power spectrum of the noisy data is not easy. Numerically, the power spectrum was calculated from $x(t)$ with 16384 data points, filtered by a Welch window. The power spectra were then smoothed by nearest averaging over 50 points, so as to estimate the peak height and width and hence SNR. These procedures were repeated on 100 independent runs to obtain the final SNR curves. The numerical results are shown in Figure 3a, and the analytical ones are shown in Figure 3b. Since the vertical axes are in arbitrary units, the absolute SNR values do not make sense. We see that qualitatively the two figures agree well with each other, that is, INCR appears and the optimal size V_{opt} and the maximal SNR both become larger when the distance from the Hopf bifurcation decreases. Our theoretical analysis reproduces the numerical results well.

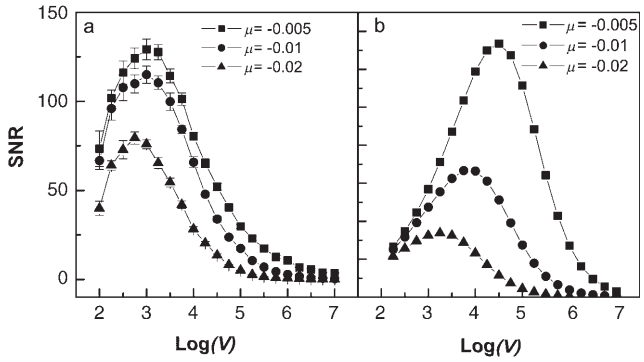

Figure 3. Dependence of the effective SNR on the system size V from a) numerical calculations and b) analytical results [Eq. (10)].

As shown in Figures 1 and 2, on decreasing the system size V (thus the internal noise level increases), the amplitude of the NIO becomes larger and the correlation time smaller. Since a longer correlation time often means more temporal "regularity", the NIO does not show a maximal regularity at an intermediate noise level. Therefore, INCR does not refer to the regularity of the NIO; but, rather, to the "performance" of it, which also accounts for the amplitude. If the noise is small, the NIO is regular but small; whereas for large noise, it is chaotic but large. Hence at an intermediate noise level, the NIO shows the best performance.

The effects of internal noise on mesoscopic chemical oscillations have also been studied by others. Specifically, Vance and Ross investigated fluctuation properties near the limit cycle in chemical reaction systems using an approximated solution to the master equation.[28] Gaspard and co-workers studied the correlation time for chemical clocks in the presence of molecular noise, also using the master equation,[29,30] and an estimation was obtained for the minimum number of molecules required for the chemical oscillations to remain correlated in time. Note that their analysis mainly focused on the parameter regions away from the Hopf bifurcation, hence NIO and INCR were not considered there. In contrast, our analysis is valid in the very vicinity of the Hopf bifurcation, where a normal form can be obtained. Therefore, combining those studies and the present work, one may be able to have a deeper understanding of the effects of internal noise in mesoscopic chemical oscillating systems.

In conclusion, we have analytically studied the NIO and INCR phenomenon observed in mesoscopic chemical reaction systems, in a parameter region subthreshold but close to the deterministic supercritical Hopf bifurcation, by normal form calculation and stochastic averaging. Numerical and analytical results show excellent agreement. Although we used the Brusselator as our model, the analysis can also apply to other systems, and we believe that NIO and INCR are common phenomena. Physically, they result from the coupling of r and θ through the internal noise associated with the reaction channels, as implied in the stochastic amplitude equation. The maximum in the effective SNR is somewhat an artificial result that arises from the definition, that is, the correlation time of the NIO does not show a maximum, rather, when we combine the amplitude and regularity of the NIO together, the "resonance" shows up. The optimal internal noise, corresponding to an optimal system size V, where the NIO shows the best performance, depends not only on common features, that is, the distance μ from the bifurcation point, but also on the specific property of the system, that is, the coefficient C_r derived from the nonlinear terms in the normal form calculation, and the deterministic steady-state values that are related to the effective intensity of the internal noise.

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[1] C. V. Rao, D. M. Wolf, A. P. Arkin, *Nature* **2002**, *420*, 231.
[2] H. Qian, S. Saffarian, E. L. Elson, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 10376.
[3] M. Kærn, T. C. Elston, W. J. Blake, J. J. Collins, *Nat. Rev. Gen.* **2005**, *6*, 451.
[4] J. M. G. Vilar, H. Y. Kueh, N. Barkai, S. Leibler, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 5988.
[5] D. Gonze, J. Halloy, A. Goldbeter, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 673.
[6] D. D. Forger, C. S. Peskin, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 321.
[7] a) J. A. White, J. T. Rubinstein, A. R. Kay, *Trends Neurosci.* **2000**, *23*, 131; b) I. Goychuk, P. Hänggi, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 3552 .
[8] M. Falcke, *Adv. Phys.* **2004**, *53*, 255.
[9] M. M. Slinko, A. A. Ukharskii, N. V. Peskov, N. I. Jaeger, *Catal. Today* **2001**, *70*, 341.
[10] N. V. Peskov, M. M. Slinko, N. I. Jaeger, *J. Chem. Phys.* **2002**, *116*, 2098.

[11] Yu. Suchorski, J. Beben, E. W. James, J. W. Evans, R. Imbihl, *Phys. Rev. Lett.* **1999**, *82*, 1907.
[12] C. H. Reichert, J. Starke, M. Eiswirth, *J. Chem. Phys.* **2001**, *115*, 4829.
[13] J. W. Shuai, P. Jung, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 506.
[14] P. Jung, J. W. Shuai, *Europhys. Lett.* **2001**, *56*, 29.
[15] a) G. Schmid, I. Goychuk, P. Hänggi, *Europhys. Lett.* **2001**, *56*, 22; b) G. Schmid, I. Goychuk, P. Hänggi, *Phys. Biol.* **2004**, *1*, 61.
[16] J. W. Shuai, P. Jung, *Phys. Rev. Lett.* **2002**, *88*, 068102.
[17] J. W. Shuai, P. Jung, *Biophys. J.* **2002**, *83*, 87.
[18] J. Q. Zhang, Z. H. Hou, H. W. Xin, *ChemPhysChem* **2004**, *5*, 1041.
[19] Z. H. Hou, H. W. Xin, *J. Chem. Phys.* **2003**, *119*, 11508.
[20] Z. H. Hou, T. Rao, H. W. Xin, *J. Chem. Phys.* **2005**, *122*, 134708.
[21] Y. B. Gong, Z. H. Hou, H. W. Xin, *J. Phys. Chem. B* **2004**, *108*, 17796.
[22] Z. H. Hou, H. W. Xin, *ChemPhysChem* **2004**, *5*, 407.
[23] J. Guckenheimer, P. Holmes, *Nonlinear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields*, Springer, New York, **1997**.
[24] N. G. Van Kapman, *Stochastic Processes in Physics and Chemistry*, North-Holland, Amsterdam, **1983**.
[25] D. T. Gillespie, *J. Chem. Phys.* **2000**, *113*, 297.
[26] C. W. Gadiner, *Handbook of Stochastic Methods for Physics, Chemistry and the Natural Sciences*, Springer, Heidelberg, **1983**.
[27] L. Arnold, N. S. Namachchivaya, K. R. Schenk-Hoppé, *Int. J. Bifurcation Chaos Appl. Sci. Eng.* **1996**, *6*, 1947.
[28] W. Vance, J. Ross, *J. Chem. Phys.* **1996**, *105*, 479.
[29] D. Gonze, J. Halloy, P. Gaspard, *J. Chem. Phys.* **2002**, *116*, 10997.
[30] P. Gaspard, *J. Chem. Phys.* **2002**, *117*, 8905.

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