

The correlation time of mesoscopic chemical clocks

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A formula is proved for the correlation time of nonequilibrium chemical clocks in the presence of molecular noise. The correlation time is defined as the inverse of the damping rate of the autocorrelation functions of the chemical concentrations. Using the Hamilton–Jacobi method for stochastic systems as well as a Legendre transform from the Onsager–Machlup action to a reduced action depending only on the Hamilton–Jacobi pseudoenergy, the correlation time is given in the weak-noise limit in terms of the extensivity parameter, the period of oscillations, as well as the derivative of the period with respect to the pseudoenergy. Using this result, an estimation is obtained for the minimum number of molecules required for the oscillations of the chemical concentrations to remain correlated in time. This estimation puts a fundamental lower limit on the size of chemical clocks. For typical oscillators, the minimum number of molecules is estimated between ten and one hundred, which essentially corresponds to nanometric systems. © 2002 American Institute of Physics. [DOI: 10.1063/1.1513461]

I. INTRODUCTION

Recently, chemical oscillations have been studied in mesoscopic systems. In particular, oscillatory behavior in the reduction of nitrogen dioxide with hydrogen has been observed on platinum by field emission microscopy.¹ In this experiment, the oscillatory behavior is directly observed on nanosized crystal facets of about 2–4 nm on the tip of the field emission microscope. The oscillatory reaction takes place over a surface area composed of several crystal facets and extending over a diameter of 10–20 nm, the period of oscillations being of about one second. In a different context, oscillatory reactions have very recently been studied in models of circadian rhythms taking place in single cells of the scale of micrometers.^{2–5} For these reactions related to the gene expression, molecular noise may be important because the number of molecules involved in the reaction is relatively small.

In such mesoscopic oscillatory reactions, we may wonder how the molecular noise affects the periodicity of the chemical clock. If the number of molecules involved in the chemical clock is too small we may expect that the molecular fluctuations are too large for the oscillations to remain correlated in time. This reasoning suggests the existence of a minimum number of molecules which is required for the system to act as a chemical clock. In order to obtain an estimation of this minimum number we first need to derive an expression for the correlation time of the noisy chemical clock.

Stochastic fluctuations such as molecular noise are known to induce a phenomenon of phase diffusion of the oscillator. As a consequence of phase diffusion, the successive oscillations are no longer in phase, leading to a loss of statistical correlation which can be characterized thanks to the time autocorrelation function of the chemical concentrations. Since the 1970s, such time autocorrelation functions

have been shown to display a damped oscillatory behavior. The stronger the stochastic fluctuations, the greater the damping of the oscillations. The inverse of the damping rate defines the correlation time of the oscillations of the chemical clock. The longer the correlation time is, the better the chemical clock is. The phenomenon of stochastic dephasing of chemical clocks has been investigated systematically in finite systems^{6–20} as well as in spatially extended systems.^{21,22} On the one hand, several methods such as the Gaussian approximation method,⁶ the Mori–Zwanzig projection method,⁷ and the Hamilton–Jacobi method¹⁷ have been developed in order to study the stochastic fluctuations around a limit cycle. On the other hand, the stationary probability distribution of the fluctuations around the limit cycle as well as the correlation time of the chemical oscillations have been explicitly calculated in particular models of chemical clocks such as the Brusselator and other models.^{8–16,18–20}

A well-known result is that the correlation time is essentially proportional to the extensivity parameter which is, for instance, the volume of the system. However, except in particular models, no sufficiently simple and general expression is known for the coefficient of proportionality between the correlation time and the extensivity parameter. In a very recent study of the influence of molecular noise on circadian rhythms⁵ a powerful expression has been given without proof for this coefficient. This expression is simple enough that it has provided an efficient method for the numerical evaluation of the correlation time of noisy circadian rhythms.⁵ It is the purpose of the present paper to give the proof of this expression for the proportionality coefficient between the correlation time and the extensivity parameter. This proof is quite subtle and delicate because it is based on an unfamiliar Legendre transform between the Onsager–Machlup action^{23,24} which depends on time, and a reduced action depending only on the pseudoenergy introduced in the Hamilton–Jacobi treatment of chemical stochastic

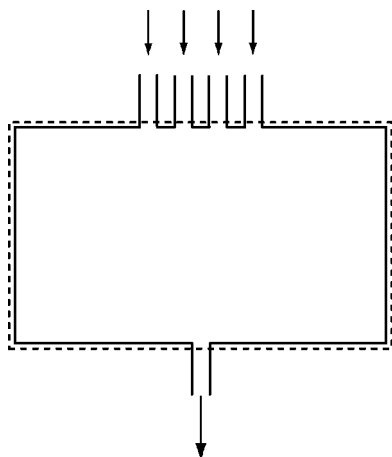


FIG. 1. Schematic representation of an open reactor with inlets and an outlet. The dashed line is the fictitious boundary inside which the number of molecules of each species is counted.

systems.^{25,26} Thanks to this Legendre transform, the correlation time of the chemical clock is expressed by a simple and elegant formula involving the derivative of the period of the oscillations with respect to the pseudoenergy of the Hamilton–Jacobi method. This formula allows us to estimate the minimum number of molecules required for the oscillations to remain correlated in time.

The paper is organized as follows. Section II gives a general introduction to the problem. The Hamilton–Jacobi method is developed in Sec. III. The aforementioned Legendre transform is performed in Sec. III B and the central result is obtained in Sec. III D. In Sec. IV, the theory is applied to the Brusselator. Conclusions are drawn in Sec. V.

II. FLUCTUATIONS IN CHEMICAL REACTIONS

A. The chemical master equation

Sustained chemical oscillations require that the reaction takes place in an open system. Such an open system is composed of some kind of container connected to the outside world by inlets through which reactants enter the system and by outlets for the exit of products. The inlets and outlets can be tubes, membranes, porous materials, or more generally the boundary between the system and the outside world. The system can moreover be submitted to other external driving thermodynamic forces such as temperature gradient or else. The system is thus delimited by a fictitious boundary (dashed line in Fig. 1) which crosses the inlets and outlets.

We denote by X^i the number of molecules of the species X^i ($i=1,2,\dots,s$) inside the system defined by the fictitious boundary. We suppose that the distribution of these molecules inside the system is essentially homogeneous, which requires that the system be of small spatial extension or that it be sufficiently well stirred such as in a continuously stirred tank reactor. The system is characterized by an extensivity parameter Ω which is, for instance its volume.

The population numbers X^i evolve in time because molecules enter the system by the inlets, react inside the system, and exit by the outlet. At the molecular level, the time evolution of the numbers X^i of molecules is a stochastic process.

First of all, the reactant molecules arrive at the boundary separating the inlets from the system at randomly distributed arrival times. Inside the system, the reacting events also occur at random because of the thermal fluctuations (and possibly also because of turbulence generated by stirring). Finally, the products cross the boundary between the system and the outlet at random exit times. The state of the reacting system inside the system is determined by the numbers $\{X^i\}$ of molecules at current time t . The overall reacting process including injection of reactants and evacuation of products can be described by the network of the reactions

$$\sum_{i=1}^s \nu_{<\rho}^i X^i \rightarrow \sum_{i=1}^s \nu_{>\rho}^i X^i \quad (1)$$

of stoichiometric coefficients $\nu_{\rho}^i = \nu_{>\rho}^i - \nu_{<\rho}^i$ with $\rho = 1, 2, \dots, r$. At a reacting event of the ρ^{th} reaction, the numbers of molecules change according to

$$\{X^i\} \rightarrow \{X^i + \nu_{\rho}^i\}. \quad (2)$$

A transition rate is associated with each reaction as²⁰

$$W_{\rho}(\{X^i\}) = \Omega k_{\rho} \prod_{i=1}^s \prod_{m=1}^{\nu_{<\rho}^i} \frac{X^i - m + 1}{\Omega}, \quad (3)$$

where k_{ρ} is the reaction rate coefficient. The transition rates have the unit of $(\text{second})^{-1}$. The transition rates are independent of time if there is no time-dependent external forcing, which we assume from now on.

The probability $P(\{X^i\}, t)$ for the system to be in the state $\{X^i\}$ at the current time t is ruled by the chemical master equation^{27–29}

$$\begin{aligned} \frac{d}{dt} P(\{X^i\}, t) = & \sum_{\rho=1}^r [W_{\rho}(\{X^i - \nu_{\rho}^i\}) P(\{X^i - \nu_{\rho}^i\}, t) \\ & - W_{\rho}(\{X^i\}) P(\{X^i\}, t)]. \end{aligned} \quad (4)$$

The normalization

$$\sum_{\{X^i\}} P(\{X^i\}, t) = 1 \quad (5)$$

of the probability distribution is constant in time according to the master equation (4). Under very general conditions, the master equation admits a stationary solution

$$\frac{d}{dt} P_{\text{st}}(\{X^i\}) = 0. \quad (6)$$

B. Eigenvalues and autocorrelation function

If the time evolution starts from a probability distribution which is not the stationary distribution P_{st} , the master equation generates a relaxation of the probability distribution toward the stationary one. Since the master equation (4) does not depend explicitly on time, the general time-dependent solution of the master equation can be decomposed in terms of the eigenvectors and other root vectors of the operator defined in the right-hand side of Eq. (4) as

$$P(\{X^i\}, t) = \sum_n c_n \Psi_n(\{X^i\}) \exp(s_n t) + (\text{Jb}), \quad (7)$$

where $\{s_n\}$ are the eigenvalues and $\{\Psi_n\}$ the associated eigenvectors. The rest (Jb) denotes the possible contributions from root vectors other than the eigenvectors, which are associated with Jordan blocks. Jordan blocks are known to appear in the spectral decomposition of a non-Hermitian operator such as the one given by Eq. (4) if some eigenvalues are degenerate.³⁰ The Jordan blocks contribute by terms of the form $t^k \exp(s_n t)$ with integer powers k strictly smaller than the multiplicity μ_n of the eigenvalue s_n . Such Jordan-block contributions do not arise in the typical case where the eigenvalues $\{s_n\}$ are not degenerate, which we assume for the master equation (4).

In Eq. (7), the coefficients $\{c_n\}$ are determined by the initial probability distribution $P(\{X^i\}, 0)$ according to

$$c_n = \sum_{\{X^i\}} P(\{X^i\}, 0) \tilde{\Psi}_n^*(\{X^i\}), \quad (8)$$

where $\tilde{\Psi}_n$ are the adjoint eigenvectors which differ in general from the eigenvectors Ψ_n in the case of non-Hermitian operators.

The conditional probability distribution that the state of the system be $\{X^i\}$ at the current time t given that the initial state was $\{X_0^i\}$ is obtained by setting $P(\{X^i\}, 0) = \prod_{i=1}^s \delta_{X^i X_0^i}$, where $\delta_{XX'} = 1$ if $X = X'$ and $\delta_{XX'} = 0$ otherwise. Therefore, the conditional probability is

$$P(\{X^i\}, t | \{X_0^i\}) = \sum_n \Psi_n(\{X^i\}) \exp(s_n t) \tilde{\Psi}_n^*(\{X_0^i\}) + (\text{Jb}). \quad (9)$$

In general, the eigenvalues $\{s_n\}$ are complex numbers and the associated eigenvectors and adjoint eigenvectors are also complex. In the spectrum of eigenvalues, we find the eigenvalue $s_0 = 0$ associated with the stationary distribution, $\Psi_0(\{X^i\}) = P_{\text{st}}(\{X^i\})$. We expect that the general solution relaxes toward the stationary distribution so that all the other eigenvalues should have a negative real part: $\text{Re } s_n < 0$ for $n \neq 0$.

The autocorrelation function of the number of molecules X^i in the system can be defined by the time average

$$C(t) \equiv \langle X^i(t) X^i(0) \rangle \equiv \lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T d\tau X^i(t + \tau) X^i(\tau). \quad (10)$$

Since the process is stationary, this time average is equal (for almost all the realizations of the stochastic process) to an average over the stationary probability distribution for the initial molecular number $X^i(0)$. In this case, we have to take the stationary distribution as the initial distribution, $P(\{X^i\}, 0) = P_{\text{st}}(\{X^i\})$ in Eqs. (7) and (8) in order to obtain the probability distribution of the molecular number $X^i(t) = X^i$ at the later time t . Using the conditional probability distribution (9), we obtain the autocorrelation function as

$$\begin{aligned} C(t) &= \langle X^i(t) X^i(0) \rangle \\ &= \sum_{\{X^i\}} \sum_{\{X_0^i\}} X^i P(\{X^i\}, t | \{X_0^i\}) X_0^i P_{\text{st}}(\{X_0^i\}) \\ &= \sum_n A_n e^{s_n t} B_n + (\text{Jb}), \end{aligned} \quad (11)$$

where

$$\begin{aligned} A_n &= \sum_{\{X^i\}} X^i \Psi_n(\{X^i\}), \\ B_n &= \sum_{\{X_0^i\}} \tilde{\Psi}_n^*(\{X_0^i\}) X_0^i P_{\text{st}}(\{X_0^i\}). \end{aligned} \quad (12)$$

If no Jordan block arises as assumed, Eq. (11) leads us to the conclusion that the autocorrelation function decays exponentially as

$$C(t) = A_0 B_0 + A_1 e^{s_1 t} B_1 + A_2 e^{s_2 t} B_2 + \cdots \quad (13)$$

with $s_0 = 0 > \text{Re } s_1 \geq \text{Re } s_2 \geq \cdots$. The long-time decay is always determined by the eigenvalues with the largest real part $\text{Re } s_n$, i.e., the eigenvalues with the smallest damping rates $-\text{Re } s_n$, which correspond to the longest decay time.

For a chemical reaction in an oscillatory regime, we should expect the existence of two nontrivial leading eigenvalues which are complex conjugate

$$\begin{aligned} s_1 &= s_2^* = -\gamma + i\omega, \\ s_2 &= s_1^* = -\gamma - i\omega. \end{aligned} \quad (14)$$

Their coefficients are also complex conjugate: $A_2 = A_1^*$ and $B_2 = B_1^*$. In this case, the autocorrelation function behaves as

$$C(t) = A_0 B_0 + 2|A_1 B_1| e^{-\gamma t} \cos[\omega t + \arg(A_1 B_1)] + \cdots \quad (15)$$

This result shows that the statistical correlations of the chemical species X^i are exponentially damped oscillations. Equation (15) allows us to identify the period of the chemical clock as

$$T = \frac{2\pi}{\omega} = \frac{2\pi}{|\text{Im } s_1|} \quad (16)$$

and its correlation time as

$$\tau = \frac{1}{\gamma} = \frac{1}{|\text{Re } s_1|} \quad (17)$$

in terms of the long-time behavior of the conditional probability (9) which is solution of the master equation (4). The purpose of Sec. II C and Sec. III is to obtain this behavior in the weak-noise limit.

C. Generalized Fokker–Planck equation

In the weak-noise limit $\Omega \rightarrow \infty$, the master equation (4) reduces to a generalized Fokker–Planck equation for the stochastic time evolution of the concentrations of the different species inside the system defined by

$$x^i \equiv \frac{X^i}{\Omega} \equiv [X^i] \quad (18)$$

with $i=1,2,\dots,s$. The probability density that these concentrations take given values is defined in terms of the probability distribution of the population numbers as

$$\mathcal{P}(\mathbf{x},t) \equiv \Omega^s P(\Omega \mathbf{x},t). \quad (19)$$

This probability density is normalized according to

$$\int \mathcal{P}(\mathbf{x},t) d\mathbf{x} = 1, \quad (20)$$

which is a consequence of the normalization (5).

Replacing the definition (19) of the probability density into the chemical master equation (4) and expanding in inverse powers of the extensivity parameter Ω , the following generalized Fokker–Planck equation is obtained

$$\begin{aligned} \frac{\partial}{\partial t} \mathcal{P}(\mathbf{x},t) = & - \sum_{j=1}^s \frac{\partial}{\partial x^j} \left\{ \left[F^j(\mathbf{x}) + \frac{1}{\Omega} G^j(\mathbf{x}) \right] \mathcal{P}(\mathbf{x},t) \right\} \\ & + \frac{1}{\Omega} \sum_{j,k=1}^s \frac{\partial^2}{\partial x^j \partial x^k} [Q^{jk}(\mathbf{x}) \mathcal{P}(\mathbf{x},t)], \end{aligned} \quad (21)$$

where we have introduced the mean drifts of the concentrations

$$F^j(\mathbf{x}) \equiv \lim_{\Omega \rightarrow \infty} \frac{1}{\Omega} \sum_{\rho=1}^r \nu_{\rho}^j W_{\rho}(\Omega \mathbf{x}) \quad (22)$$

with its corrections

$$G^j(\mathbf{x}) \equiv \lim_{\Omega \rightarrow \infty} \left[\sum_{\rho=1}^r \nu_{\rho}^j W_{\rho}(\Omega \mathbf{x}) - \Omega F^j(\mathbf{x}) \right] \quad (23)$$

and the matrix of diffusivity

$$Q^{jk}(\mathbf{x}) \equiv \lim_{\Omega \rightarrow \infty} \frac{1}{2\Omega} \sum_{\rho=1}^r \nu_{\rho}^j \nu_{\rho}^k W_{\rho}(\Omega \mathbf{x}). \quad (24)$$

The diffusivity matrix is symmetric and nonnegative.

In Eq. (21), the terms of degrees Ω^{-2} , Ω^{-3} ,... are neglected because we are interested in the leading behavior of the solution in the weak-noise limit $\Omega \rightarrow \infty$. This assumption is justified under the condition that the corresponding macroscopic system does not undergo a bifurcation such as a Hopf bifurcation. Away from bifurcations, the fluctuations are expected to remain of Gaussian character around the macroscopic trajectory and this Gaussian behavior is well described by the generalized Fokker–Planck equation (21). In the weak-noise limit, the solution of the generalized Fokker–Planck equation (21) would thus provide a good approximation for the solution of the chemical master equation (4) under the aforementioned conditions. It should be emphasized that this approximation is not valid in the vicinity of a bifurcation destabilizing the limit cycle where a different method is required as discussed in the literature.^{31,32} Here, we suppose that the limit cycle is not undergoing a bifurcation in order to remain in the domain of validity of the approximation (21).

III. THE CORRELATION TIME IN THE WEAK-NOISE LIMIT

A. Hamilton–Jacobi equation

In the weak-noise limit $\Omega \rightarrow \infty$, the solution of the generalized Fokker–Planck equation (21) can be expressed in the following form:^{17,25,26,33–35}

$$\begin{aligned} \mathcal{P}(\mathbf{x},t) = \exp \left[-\Omega \phi_0(\mathbf{x},t) - \phi_1(\mathbf{x},t) - \frac{\phi_2(\mathbf{x},t)}{\Omega} \right. \\ \left. - \frac{\phi_3(\mathbf{x},t)}{\Omega^2} - \dots \right]. \end{aligned} \quad (25)$$

Near the thermodynamic equilibrium and in the weak-noise limit $\Omega \rightarrow \infty$, the leading function ϕ_0 can be interpreted in terms of the excess entropy ΔS associated with the fluctuations according to $\phi_0 \approx -\Delta S/k_B \Omega$.

We can here introduce the momenta $\mathbf{p} = \{p_i\}$ which are associated with the chemical concentrations $\mathbf{x} = \{x^i\}$ as

$$p_i \equiv \frac{\partial \phi_0}{\partial x^i} \quad (i=1,2,\dots,s). \quad (26)$$

These momenta are proportional to the thermodynamic forces.

Replacing the expression (25) in the generalized Fokker–Planck equation (21) and identifying the terms with the same power in the extensivity parameter Ω , we obtain a hierarchy of coupled equations. The leading equation is the following Hamilton–Jacobi equation:

$$\frac{\partial \phi_0}{\partial t} + H\left(\mathbf{x}, \frac{\partial \phi_0}{\partial \mathbf{x}}\right) = 0 \quad (27)$$

with the special Hamiltonian^{33,34}

$$H(\mathbf{x},\mathbf{p}) = \sum_{j,k=1}^s Q^{jk}(\mathbf{x}) p_j p_k + \sum_{j=1}^s F^j(\mathbf{x}) p_j. \quad (28)$$

This Hamiltonian function is known to correspond to the Lagrangian function of Onsager and Machlup.^{23,24}

The general solution of the Hamilton–Jacobi equation (27) can be written as the action

$$\phi_0(\mathbf{x},t) = \int \mathbf{p} \cdot d\mathbf{x} - H dt, \quad (29)$$

where the integral is carried out over the trajectories of Hamilton's equations:

$$\begin{aligned} \dot{x}^i &= + \frac{\partial H}{\partial p_i} = F^i(\mathbf{x}) + 2 \sum_{j=1}^s Q^{ij}(\mathbf{x}) p_j, \\ \dot{p}_i &= - \frac{\partial H}{\partial x^i} = - \sum_{j,k=1}^s \frac{\partial F^j(\mathbf{x})}{\partial x^i} p_j - \sum_{j,k=1}^s \frac{\partial Q^{jk}(\mathbf{x})}{\partial x^i} p_j p_k. \end{aligned} \quad (30)$$

We notice that the subspace $\mathbf{p} = \mathbf{0}$ of vanishing momenta is invariant for the special Hamiltonian system (30). This invariant subspace contains the macroscopic trajectories. Indeed, Hamilton's equations (30) reduce to the macroscopic equations of chemical kinetics when $\mathbf{p} = \mathbf{0}$:

$$\dot{x}^i = F^i(\mathbf{x}) = \sum_{\rho=1}^r v_{\rho}^i w_{\rho}(\mathbf{x}) \quad \text{in } \mathbf{p}=\mathbf{0} \quad (31)$$

with the reaction rates

$$w_{\rho}(\mathbf{x}) \equiv \lim_{\Omega \rightarrow \infty} \frac{1}{\Omega} W_{\rho}(\Omega \mathbf{x}) = k_{\rho} \prod_{i=1}^s (x^i)^{v_{\rho}^i} \quad (32)$$

in agreement with the mass-action law.

B. Legendre transform

Since the system is not submitted to time-dependent forcing the Hamiltonian function (28) is time independent so that it is conserved along the trajectories of Hamilton's equations (30):

$$\frac{dH}{dt} = 0. \quad (33)$$

As a consequence, the pseudoenergy

$$E = H(\mathbf{x}, \mathbf{p}) \quad (34)$$

is a constant of motion for Hamilton's equations (30). This pseudoenergy has the units of the extensivity parameter Ω divided by a time. Accordingly, the quantity E/Ω should be interpreted as a rate.

If the pseudoenergy is conserved, the action (29) can be written as

$$\phi_0(\mathbf{x}, t) = V(\mathbf{x}, E) - Et \quad (35)$$

in terms of the reduced action

$$V(\mathbf{x}, E) = \int \mathbf{p} \cdot d\mathbf{x} \quad (36)$$

defined for trajectories belonging to the pseudoenergy shell (34).

The functions $\phi_0(\mathbf{x}, t)$ and $V(\mathbf{x}, E)$ are related by a Legendre transform. On the one hand, the action ϕ_0 should be independent of pseudoenergy so that

$$\frac{\partial \phi_0}{\partial E} = \frac{\partial V}{\partial E} - t = 0. \quad (37)$$

On the other hand, the reduced action V is independent of time so that

$$\frac{\partial V}{\partial t} = \frac{\partial \phi_0}{\partial t} + E = 0. \quad (38)$$

Accordingly, the time spent on a trajectory segment at pseudoenergy E is given by

$$t = \frac{\partial V}{\partial E} \quad (39)$$

and the pseudoenergy of a trajectory segment of action ϕ_0 by

$$E = - \frac{\partial \phi_0}{\partial t}. \quad (40)$$

The second derivative of the action with respect to the time is thus remarkably given in terms of the derivative of the time duration t with respect to the pseudoenergy E as

$$\frac{\partial^2 \phi_0}{\partial t^2} = - \frac{\partial E}{\partial t} = - \left(\frac{\partial t}{\partial E} \right)^{-1}. \quad (41)$$

This formula is essential for the proof of our central result below.

C. Expansion around a limit cycle

For a chemical clock, the macroscopic system (31) admits a limit cycle or periodic attractor, which is a stable periodic solution of some prime period T :

$$\mathbf{x}(t + rT) = \mathbf{x}(t) \quad \text{for } r = 0, \pm 1, \pm 2, \pm 3, \dots \quad (42)$$

belonging to the subspace $\mathbf{p}=\mathbf{0}$. The integer r is the repetition number of the prime period T . We can here introduce the phase θ of a point on the limit cycle as the time interval from a point of origin $\mathbf{x}(0)$ on the cycle up to the current point $\mathbf{x}(\theta)$. Therefore, the phase belongs to the interval $0 \leq \theta < T$.

It is important to notice that the limit cycle (42) has a continuation outside the invariant subspace $\mathbf{p}=\mathbf{0}$ into a deformed cycle which is still a periodic solution of Hamilton's equations (30). The deformed cycle at $\mathbf{p} \neq \mathbf{0}$ has a different period $\mathcal{T}(E)$ which depends on the pseudoenergy and which reduces to the macroscopic period in the invariant subspace $\mathbf{p}=\mathbf{0}$ where $E=0$: $\mathcal{T}(E=0) = T$.

For our purpose, we need an approximation for the conditional probability (9) that the concentrations take the values \mathbf{x} at current time t given that their initial conditions are \mathbf{x}_0 . For simplicity, we suppose that the initial conditions belong to the macroscopic limit cycle: $\mathbf{x}_0 = \mathbf{x}(\theta_0)$. Moreover, we suppose that the final point \mathbf{x} is close to a point \mathbf{x}_* of the macroscopic limit cycle that is reached at time t_* : $\mathbf{x}_* = \mathbf{x}(t_*)$. The time t_* is given by

$$t_* = rT + \theta_* - \theta_0, \quad (43)$$

where θ_* is the phase of the point $\mathbf{x}_* = \mathbf{x}(\theta_*)$ and r is an integer. We suppose that both phases θ_0 and θ_* are real numbers which are *a priori* given.

The action (29) can be expanded in Taylor series around the point \mathbf{x}_* and the corresponding time t_* to get

$$\begin{aligned} \phi_0(\mathbf{x}, t) = & \phi_0(\mathbf{x}_*, t_*) + \frac{\partial \phi_0(\mathbf{x}_*, t_*)}{\partial t} (t - t_*) \\ & + \frac{\partial \phi_0(\mathbf{x}_*, t_*)}{\partial \mathbf{x}} \cdot (\mathbf{x} - \mathbf{x}_*) + \frac{1}{2} \frac{\partial^2 \phi_0(\mathbf{x}_*, t_*)}{\partial t^2} \\ & \times (t - t_*)^2 + \frac{\partial^2 \phi_0(\mathbf{x}_*, t_*)}{\partial t \partial \mathbf{x}} \cdot (\mathbf{x} - \mathbf{x}_*) (t - t_*) \\ & + \frac{1}{2} \frac{\partial^2 \phi_0(\mathbf{x}_*, t_*)}{\partial \mathbf{x}^2} : (\mathbf{x} - \mathbf{x}_*)^2 + \dots, \end{aligned} \quad (44)$$

neglecting terms of cubic and higher degrees. This truncation is consistent with our assumption that the limit cycle is not bifurcating and the fluctuations are essentially of Gaussian character.

Since the point (\mathbf{x}_*, t_*) belongs to the macroscopic limit cycle, both its momenta and pseudoenergy vanish. According to Eq. (29), the action itself vanishes. The second equations

of Hamilton (30) show that the time derivative $\dot{\mathbf{p}}$ also vanishes at $\mathbf{p}=\mathbf{0}$. Moreover, in order to apply Eq. (41) to the time (43), we need the derivative of the time duration with respect to the pseudoenergy which is given by

$$\frac{\partial t_*}{\partial E} = r \frac{\partial T}{\partial E} \bigg|_{E=0} = r \frac{\partial T}{\partial E}. \quad (45)$$

Hence, we obtain the following results:

$$\phi_0(\mathbf{x}_*, t_*) = 0, \quad (46)$$

$$\frac{\partial \phi_0(\mathbf{x}_*, t_*)}{\partial t} = -E = 0, \quad (47)$$

$$\frac{\partial \phi_0(\mathbf{x}_*, t_*)}{\partial \mathbf{x}} = \mathbf{p} = \mathbf{0}, \quad (48)$$

$$\frac{\partial^2 \phi_0(\mathbf{x}_*, t_*)}{\partial t \partial \mathbf{x}} = \dot{\mathbf{p}} = -\frac{\partial H}{\partial \mathbf{x}} = \mathbf{0}, \quad (49)$$

$$\frac{\partial^2 \phi_0(\mathbf{x}_*, t_*)}{\partial t^2} = -\frac{1}{r \partial T / \partial E}. \quad (50)$$

We notice that the action function ϕ_0 appearing in the probability density should present a maximum on the macroscopic limit cycle at $\mathbf{x}=\mathbf{x}_*$ and $t=t_*$. As a consequence, the second derivative (50) must be positive, which implies that the derivative of the period with respect to the pseudoenergy is negative:

$$\frac{\partial T}{\partial E} = -\left| \frac{\partial T}{\partial E} \right| < 0. \quad (51)$$

As a consequence of the previous results, the action function has the following expansion around the macroscopic limit cycle:

$$\begin{aligned} \phi_0(\mathbf{x}, t) = & \frac{1}{2r|\partial T/\partial E|} (t-t_*)^2 \\ & + \frac{1}{2} \frac{\partial^2 \phi_0(\mathbf{x}_*, t_*)}{\partial \mathbf{x}^2} : (\mathbf{x}-\mathbf{x}_*)^2 + \dots \end{aligned} \quad (52)$$

Replacing into the probability density (25) we obtain the conditional probability density to reach the point \mathbf{x} starting from the initial conditions \mathbf{x}_0

$$\begin{aligned} \mathcal{P}(\mathbf{x}, t | \mathbf{x}_0) \sim & \exp \left[-\frac{\Omega}{2r|\partial T/\partial E|} (t-t_*)^2 \right. \\ & \left. - \frac{\Omega}{2} \frac{\partial^2 \phi_0(\mathbf{x}_*, t_*)}{\partial \mathbf{x}^2} : (\mathbf{x}-\mathbf{x}_*)^2 \right], \end{aligned} \quad (53)$$

which holds for $t_* - T/2 < t < t_* + T/2$ in the weak-noise limit $\Omega \rightarrow \infty$. Equation (53) shows that the fluctuations are of Gaussian character around the limit cycle.

We remark that the distribution of probability transverse to the limit cycle should be of the order $\Omega^{-1/2}$ in the limit $t \rightarrow \infty$. The transverse extension of the probability distribution should not depend significantly on the time but depends on the stability of the limit cycle: the stronger the stability, the sharper the distribution. In contrast, the distribution of probability longitudinal to the limit cycle becomes broader

and broader as $(t/\Omega)^{1/2}$ in the limit $t \rightarrow \infty$ because $r \approx t/T$. This broadening of the distribution longitudinal to the cycle is the effect of phase diffusion. Therefore, the phase diffusion is the dominant effect whereupon we can approximate the conditional probability density in phase by

$$\begin{aligned} \mathcal{P}(\theta, t | \theta_0) \approx & \sqrt{\frac{\Omega}{2\pi r|\partial T/\partial E|}} \exp \left\{ -\frac{\Omega}{2r|\partial T/\partial E|} \right. \\ & \left. \times [\theta - (\theta_0 + t - rT)]^2 \right\} \end{aligned} \quad (54)$$

for $-T/2 < \theta - (\theta_0 + t - rT) < T/2$ in the weak-noise limit. Here, we suppose that the final point is close enough to the limit cycle that it can be determined by the corresponding phase θ according to $\mathbf{x}(\theta) = \mathbf{x}$. We note that the conditional probability density (54) reduces to the Dirac distribution in the deterministic limit

$$\lim_{\Omega \rightarrow \infty} \mathcal{P}(\theta, t | \theta_0) = \delta(\theta - (\theta_0 + t - rT)), \quad (55)$$

as it should.

Furthermore, the stationary probability distribution has the form $\mathcal{P}_{\text{st}}(\theta) = 1/T$ for $0 \leq \theta < T$, under the same approximations.

D. The correlation time of a noisy limit cycle

The autocorrelation function (11) can be expressed in terms of the chemical concentrations as

$$\begin{aligned} C(t) = & \Omega^2 \langle x^i(t) x^i(0) \rangle \\ = & \Omega^2 \int d\mathbf{x} d\mathbf{x}_0 x^i \mathcal{P}(\mathbf{x}, t | \mathbf{x}_0) x_0^i \mathcal{P}_{\text{st}}(\mathbf{x}_0). \end{aligned} \quad (56)$$

In the weak-noise limit $\Omega \rightarrow \infty$ and under the assumption that the transverse distribution is less important than the longitudinal distribution, we can substitute the conditional probability density (54) into Eq. (56) to obtain

$$\begin{aligned} C(t) \approx & \Omega^2 \int_0^T d\theta \int_0^T d\theta_0 x^i(\theta) \mathcal{P}(\theta, t | \theta_0) \\ & \times x^i(\theta_0) \mathcal{P}_{\text{st}}(\theta_0). \end{aligned} \quad (57)$$

We expand in Fourier series the limit-cycle solution of the macroscopic equations (31) as

$$x^i(\theta) = \sum_{n=-\infty}^{+\infty} a_n \exp \left(i \frac{2\pi n}{T} \theta \right). \quad (58)$$

We replace the Fourier expansion (58) as well as the approximation (54) into Eq. (57) and we perform the integrals in the weak-noise limit $\Omega \rightarrow \infty$. Moreover, we replace the repetition number by its continuous-time approximation, $r \approx t/T$. We finally obtain the autocorrelation function as

$$\begin{aligned} C(t) \approx & \Omega^2 \sum_{n=-\infty}^{+\infty} |a_n|^2 \exp \left(i \frac{2\pi n}{T} t \right) \\ & \times \exp \left[-\frac{\left| \frac{\partial T}{\partial E} \right|}{2\Omega T} \left(\frac{2\pi n}{T} \right)^2 t \right] \end{aligned} \quad (59)$$

for $t > 0$.

We can identify the eigenvalues by comparing with Eq. (11). In this way, we obtain approximate values for the eigenvalues in the weak-noise limit as

$$s_n = i \frac{2\pi n}{T} - \frac{|\partial T / \partial E|}{2\Omega T} \left(\frac{2\pi n}{T} \right)^2 + \mathcal{O}\left(\frac{1}{\Omega^2}\right) \quad (60)$$

with $n = 0, \pm 1, \pm 2, \pm 3, \dots$

The eigenvalue with $n=0$ is associated with the stationary state since $s_0=0$. The leading nontrivial eigenvalues are given for $n = \pm 1$ by

$$s_1 = s_{-1}^* = i \frac{2\pi}{T} - \frac{|\partial T / \partial E|}{2\Omega T} \left(\frac{2\pi}{T} \right)^2 + \mathcal{O}\left(\frac{1}{\Omega^2}\right), \quad (61)$$

which provide us with the pulsation ω and the damping rate γ of the autocorrelation function according to Eq. (14). As a conclusion, we obtain our central result that the correlation time of the chemical clock is given by

$$\tau \simeq \frac{\Omega T^3}{2\pi^2 |\partial T / \partial E|} \quad (62)$$

in the weak-noise limit $\Omega \rightarrow \infty$.

Beside the well-known proportionality in the extensivity parameter Ω , we have obtained a general expression for the coefficient of proportionality in terms of the period T and the derivative of the period with respect to the pseudoenergy $E = H$ associated with the Hamilton–Jacobi equation. The derivative $\partial T / \partial E$ can be calculated by considering perturbations with $\mathbf{p} \neq \mathbf{0}$ evolving under Hamilton's equations (30) around the macroscopic limit cycle, as shown elsewhere.^{5,36} The formula (62) can be applied in the weak-noise limit to different kinds of stochastic systems which are described by a Fokker–Planck equation. This formula is simple and elegant because it only involves the dependence of the period on the pseudoenergy, beside the extensivity parameter.

An important consequence of the formula (62) is that it provides an estimation for the minimum number of molecules which is required in order for the reacting system to act as a chemical clock and, hence, to produce correlated oscillations. Indeed, we can say that the successive oscillations remain correlated in time under the condition that the correlation time is longer than the fraction $1/(2\pi)$ of the period of the oscillations:

$$\omega\tau = \frac{2\pi\tau}{T} \simeq \frac{\Omega T^2}{\pi |\partial T / \partial E|} > 1. \quad (63)$$

This condition is fulfilled if the extensivity parameter Ω exceeds the critical value

$$\Omega_c = \frac{\pi}{T^2} \left| \frac{\partial T}{\partial E} \right|. \quad (64)$$

Therefore, the oscillations remain correlated if the total number of molecules in the system satisfies

$$N = \sum_{i=1}^s X^i > \Omega_c \left(\sum_{i=1}^s x^i \right)_{\max} = \frac{\pi}{T^2} \left| \frac{\partial T}{\partial E} \right| \left(\sum_{i=1}^s x^i \right)_{\max} \equiv N_{\min}, \quad (65)$$

where $(\sum_{i=1}^s x^i)_{\max}$ denotes the maximum value of the sum of concentrations during one oscillation. The minimum total number N_{\min} of molecules in Eq. (65) depends not only on the characteristic quantities of the macroscopic limit cycle but also on those of the molecular fluctuations, because the pseudoenergy E is given by the Hamiltonian (28), which depends on the noise amplitude controlled by the diffusivity matrix (24). In order to evaluate the minimum number of molecules in a typical chemical clock, Eq. (65) will be applied to the Brusselator in Sec. IV. We notice that, for a system of minimum size (65), the fluctuations transverse to the limit cycle can be as large as the cycle itself, which may further decorrelate the oscillations.

E. The correlation time of a noisy steady state

It is interesting to compare the case of a noisy oscillation with the case of a noisy steady state, which is our purpose in the present subsection. If the chemical reaction is in a stable macroscopic steady regime (i.e., a steady attractor), the probability density is of Gaussian character around the macroscopic concentrations of the steady state given by

$$\dot{\mathbf{x}} = \mathbf{F}(\mathbf{x}_s) = 0 \quad \text{and} \quad \mathbf{p} = \mathbf{0}. \quad (66)$$

Under the effect of molecular noise, the concentrations fluctuate around their average value \mathbf{x}_s . The autocorrelation function of these fluctuations is exponentially damped with rates given by the eigenvalues of linear stability of the macroscopic steady state. This result can be obtained by solving the generalized Fokker–Planck equation (21) around a steady state of Hamilton's equations (30) in the weak-noise limit.³⁶ The stability of the macroscopic steady state is studied by linearizing the macroscopic equations (31)

$$\delta \dot{\mathbf{x}} = \frac{\partial \mathbf{F}}{\partial \mathbf{x}}(\mathbf{x}_s) \cdot \delta \mathbf{x}. \quad (67)$$

The eigenvalues of linear stability are given by the roots of the characteristic determinant

$$\det \left[\frac{\partial \mathbf{F}}{\partial \mathbf{x}}(\mathbf{x}_s) - \xi \mathbf{I} \right] = 0. \quad (68)$$

Since this determinant is a polynomial in ξ with real coefficients, its roots are either real numbers or form pairs of complex conjugate numbers. For a stable steady state the eigenvalues ξ satisfy

$$0 > \lambda_1 = \text{Re } \xi_1 \geq \lambda_2 = \text{Re } \xi_2 \geq \dots, \quad (69)$$

where $\lambda_i = \text{Re } \xi_i$ are the so-called Lyapunov exponents.

The autocorrelation function has thus the following dependence

$$C(t) = \Omega^2 \langle x^i(t) x^i(0) \rangle \simeq C_0 + C_1 \exp(\xi_1 t) + C_2 \exp(\xi_2 t) + \dots \quad (70)$$

TABLE I. Transition rates (3) and reaction rates (32) for the Brusselator (72).

Transition rate	Reaction rate
$W_1=k_1\Omega$	$w_1=k_1$
$W_2=k_2X$	$w_2=k_2x$
$W_3=k_3\frac{X(X-1)Y}{\Omega^2}$	$w_3=k_3x^2y$
$W_4=k_4X$	$w_4=k_4x$

with possible corrections in powers of Ω^{-1} added to the macroscopic eigenvalues ξ_i .

Two cases are to be considered:

(1) If the leading eigenvalue is real, the autocorrelation function presents a monotonic exponential damping at long times. In this first case, the damping rate is approximately given by $\lambda_1=\xi_1$.

(2) If the leading eigenvalue is complex, its complex conjugate is also an eigenvalue so that the autocorrelation function presents exponentially damped oscillations at long time. In this second case, the damping rate is approximately given by $\lambda_1=\text{Re } \xi_1$ again and the period of oscillations by $T\approx 2\pi/|\text{Im } \xi_1|$.

In both cases, the correlation time is given in terms of the maximum Lyapunov exponent of the macroscopic steady state as

$$\tau=\frac{1}{|\lambda_1|}+\mathcal{O}\left(\frac{1}{\Omega}\right)=\frac{1}{|\text{Re } \xi_1|}+\mathcal{O}\left(\frac{1}{\Omega}\right) \tag{71}$$

for a nonbifurcating steady state with $\lambda_1<0$. This result shows that, for a noisy steady state, the correlation time (71) becomes independent of the extensivity parameter Ω in the weak-noise limit $\Omega\rightarrow\infty$, in sharp contrast with the correlation time (62) of a noisy limit cycle that diverges as Ω in the weak-noise limit. The origin of this divergence holds in the fact that the maximum Lyapunov exponent of a stable limit cycle is equal to zero, so that the nonequilibrium oscillator can remain correlated over an arbitrarily long time interval in the macroscopic limit.

IV. APPLICATION TO THE BRUSSELATOR

A. Definition of the system

In order to verify the results of the previous sections we consider a simple model of chemical clock which is the Brusselator:³⁷



The transition rates and the reaction rates are given in Table I. The matrix of stoichiometric coefficients is given by

$$i \backslash \rho \quad \begin{array}{cccc} 1 & 2 & 3 & 4 \end{array}$$
$$[\nu_{\rho}^i]_{i=x,y;\rho=1,2,3,4} = \begin{array}{c} x \\ y \end{array} \begin{pmatrix} +1 & -1 & +1 & -1 \\ 0 & +1 & -1 & 0 \end{pmatrix} \tag{73}$$

so that the macroscopic vector field (31) is inferred to be

$$F_x=w_1-w_2+w_3-w_4=k_1-k_2x+k_3x^2y-k_4x, \tag{74}$$

$$F_y=w_2-w_3=k_2x-k_3x^2y, \tag{75}$$

and the diffusivity matrix (24)

$$Q_{xx}=\frac{1}{2}(w_1+w_2+w_3+w_4), \tag{76}$$

$$Q_{xy}=Q_{yx}=\frac{1}{2}(-w_2-w_3), \tag{77}$$

$$Q_{yy}=\frac{1}{2}(w_2+w_3). \tag{78}$$

B. Prediction for the correlation time of fluctuations

The macroscopic steady state is located at

$$x_s=\frac{k_1}{k_4} \quad \text{and} \quad y_s=\frac{k_2}{k_1}\frac{k_4}{k_3}. \tag{79}$$

The stability eigenvalues of the steady state (79) are $\xi=\lambda+i\omega$ where the Lyapunov exponent λ and pulsation ω are given by

$$\lambda=\frac{k_2-k_{2,c}}{2}, \tag{80}$$

$$\omega=\sqrt{\frac{k_1^2k_3}{k_4}-\left(\frac{k_2-k_{2,c}}{2}\right)^2}, \tag{81}$$

with the critical parameter

TABLE II. Period T , negative Lyapunov exponent λ_2 , derivative $\partial T/\partial E$, and correlation time τ given by Eq. (62) for the limit cycle of the Brusselator (72) in the case where $k_1=0.5$, $k_3=k_4=1$, and $k_2>k_{2,c}=1.25$. The correlation time is calculated for the extensivity parameter $\Omega=1000$. We notice that the maximum Lyapunov exponent of the limit cycle vanishes $\lambda_1=0$.

k_2	T	λ_2	$\partial T/\partial E$	τ
1.2625	12.685	-0.0129	-19196.4	5.39
1.275	12.809	-0.0265	-10501.7	10.14
1.30	13.071	-0.0562	-6231.2	18.16
1.35	13.644	-0.1273	-4088.4	31.48
1.40	14.238	-0.2145	-3022.5	48.38
1.45	14.764	-0.3115	-2114.9	77.08
1.50	15.163	-0.4073	-1519.3	116.25
1.55	15.445	-0.4955	-1205.4	154.85
1.60	15.650	-0.5751	-1038.9	186.92
1.65	15.815	-0.6479	-943.2	212.46
1.70	15.964	-0.7162	-886.2	232.57
1.75	16.111	-0.7815	-853.8	248.14
1.80	16.264	-0.8452	-838.4	259.99

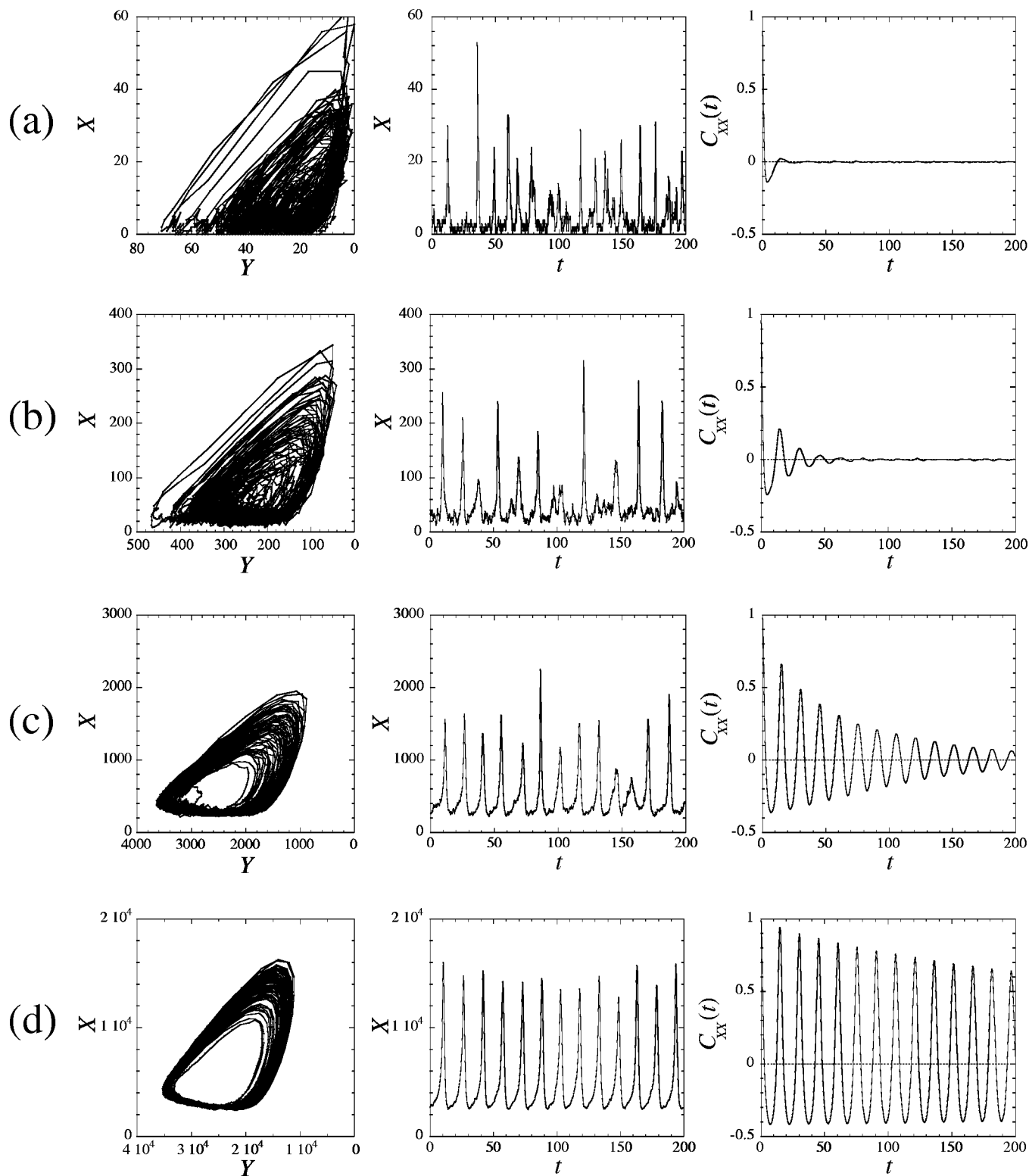


FIG. 2. Simulations of the Brusselator in the oscillatory regime by Gillespie's algorithm for the parameter values $k_1=0.5$, $k_2=1.5$, $k_3=k_4=1$. From top to bottom, the extensivity parameter takes the values: (a) $\Omega=10$, (b) $\Omega=100$, (c) $\Omega=1000$, and (d) $\Omega=10\,000$. The first column shows phase portraits in the plane of the number of molecules of species X and Y . The second column shows the number of molecules X as a function of time. The third column shows the autocorrelation function of the number of molecules X , normalized to unity.

$$k_{2,c} = k_4 + \frac{k_1^2 k_3}{k_4^2}. \quad (82)$$

$$\tau \approx \frac{1}{|\lambda|} = \frac{2}{|k_2 - k_{2,c}|} \quad (83)$$

For $k_2 < k_{2,c}$, the steady state is a stable focus of period T as predicted by Eq. (71).

$= 2\pi/\omega$ with the pulsation (81) and the correlation time

At the critical value $k_2 = k_{2,c}$, the stable focus undergoes

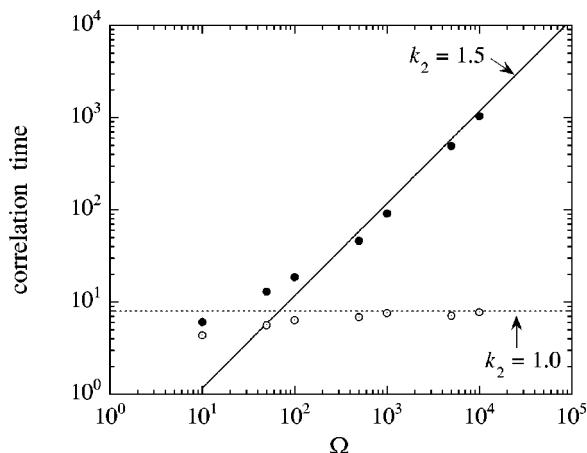


FIG. 3. Correlation time of the Brusselator with $k_1=0.5$ and $k_3=k_4=1$ vs the extensivity parameter Ω in the steady regime at $k_2=1.0 < k_{2,c}$ and in the oscillatory regime at $k_2=1.5 > k_{2,c}$.

a Hopf bifurcation which is at the origin of oscillatory behavior. We have no prediction for the correlation time near the Hopf bifurcation in the present paper.

For $k_2 > k_{2,c}$, a limit cycle exists that is stable. In this oscillatory regime, the correlation time is predicted to take the value (62), which can be computed numerically as explained elsewhere.^{5,36} The values of the period T , its derivative $\partial_E T$, and the negative Lyapunov exponent of the limit cycle, as well as the correlation time are given in Table II in the case where $k_1=0.5$ and $k_3=k_4=1$. In this case, the Hopf bifurcation occurs at $k_{2,c}=1.25$. The extensivity parameter is chosen to the value $\Omega=1000$.

C. Numerical simulations

The stochastic process associated with the master equation (4) has been simulated by Gillespie's algorithm.^{38,39} Figure 2 depicts the behavior of the process in the oscillatory regime for different values of the extensivity parameter. We

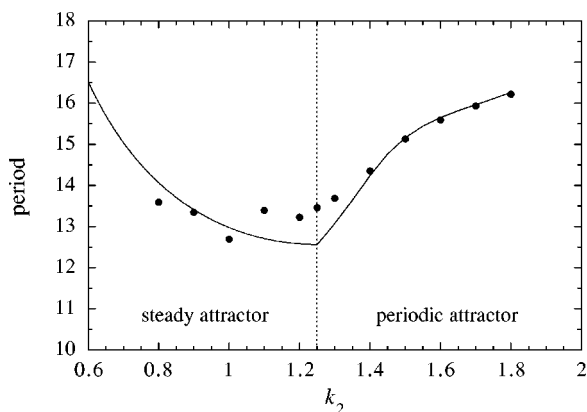


FIG. 4. Period (dots) of the oscillations in the time autocorrelation function vs the parameter k_2 for the Brusselator with $k_1=0.5$, $k_3=k_4=1$, and the extensivity parameter $\Omega=1000$. The solid lines are the predictions (see text). The vertical dashed line indicates the locus of the Hopf bifurcation at $k_{2,c}=1.25$.

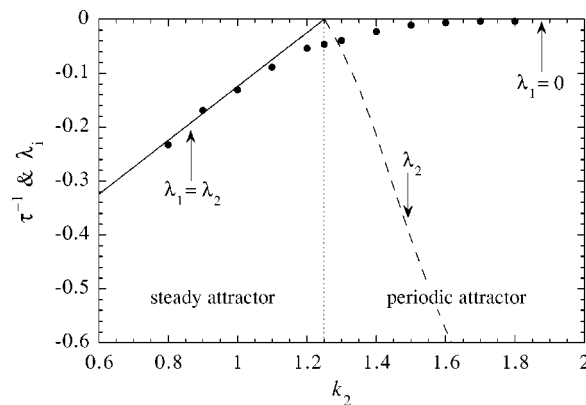


FIG. 5. Damping rate τ^{-1} (dots) of the autocorrelation function $C_{xx}(t)$ and Lyapunov exponents of the attractor vs the parameter k_2 for the Brusselator with $k_1=0.5$, $k_3=k_4=1$, and the extensivity parameter $\Omega=1000$. The solid line is the Lyapunov exponent $\lambda=\lambda_1$ of the steady state given by Eq. (80) and the long dashed line is the minimum Lyapunov exponents λ_2 of the limit cycle given in Table II. The vertical dashed line indicates the locus of the Hopf bifurcation at $k_{2,c}=1.25$.

observe that the autocorrelation function has a shorter and shorter correlation time as the extensivity parameter decreases.

Figure 3 depicts the correlation time versus the extensivity parameter Ω before and after the Hopf bifurcation. We observe that, in the steady regime before the Hopf bifurcation, the correlation time becomes independent of Ω in the limit $\Omega \rightarrow \infty$, as predicted by Eq. (71). On the other hand, the correlation time is proportional to Ω in the oscillatory regime after the Hopf bifurcation, as predicted by Eq. (62).

Figure 4 shows the period of the damped oscillations compared to the prediction $T=2\pi/\omega$ with the pulsation (81) in the steady regime, and to the values of the period given in Table II in the oscillatory regime.

Figure 5 depicts the damping rate of the autocorrelation function (i.e., the inverse of the correlation time of the fluctuations) in comparison with the Lyapunov exponents of the steady state in the steady regime and of the limit cycle in the oscillatory regime. We observe that the damping rate remains close to the maximum Lyapunov exponent in both regimes, in agreement with the expectation. The agreement is better

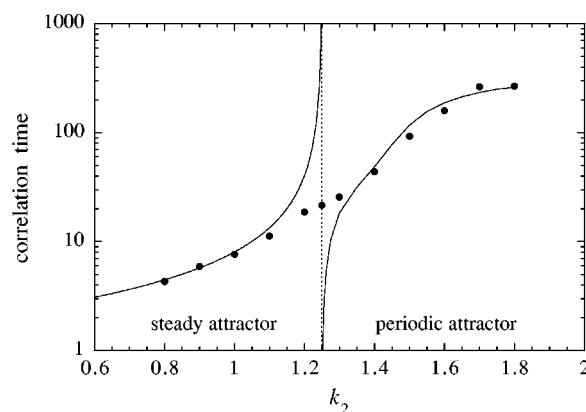


FIG. 6. Correlation time of the time autocorrelation function (dots) vs the parameter k_2 for the Brusselator with $k_1=0.5$, $k_3=k_4=1$, and the extensivity parameter $\Omega=1000$. The solid lines are the predictions by Eqs. (71) and (62). The vertical dashed line indicates the locus of the Hopf bifurcation at $k_{2,c}=1.25$.

away from the Hopf bifurcation where the fluctuations have a smaller effect.

Figure 6 depicts the correlation time of the fluctuations in comparison with the prediction of Eqs. (71) and (62) in the steady and oscillatory regimes. We observe that the correlation time is given by the inverse of the maximum Lyapunov exponent in the steady regime as predicted by Eq. (71). As the Hopf bifurcation is approached the maximum Lyapunov exponent vanishes, although the correlation time remains finite. We observe a turnover to the oscillatory regime. (This turnover is not described by the theory developed in the present paper, as said above.) After the bifurcation, the correlation time is in good agreement with the prediction of Eq. (62) again away from the bifurcation itself. This comparison verifies the predictions of the present theory in its domain of validity.

In Fig. 2, we observe that the autocorrelation function is strongly damped for a small value of the extensivity parameter such as $\Omega = 10$. This feature can be explained by computing the critical value (64) of the extensivity parameter below which the oscillations are no longer correlated. According to Table II, for $k_2 = 1.5$, the period is $T \approx 15.2$ and $\partial_E T \approx -1519.3$ so that the critical value is $\Omega_c = \pi |\partial_E T| / T^2 \approx 21$, in agreement with the observation of Fig. 2. Since $(x + y)_{\max} \approx 3.9$, the minimum total number of molecules (65) for correlated oscillations is given by $N_{\min} = (X + Y)_{\min} \approx 82$. This result shows that the chemical oscillator should contain at least about 82 molecules in order to oscillate properly.

V. CONCLUSIONS

In the present paper, we have studied the effect of molecular fluctuations on a nonequilibrium system sustaining an oscillatory reaction. First of all, we have given the complete proof of a general expression for the correlation time of a noisy chemical clock. This expression has already been presented without proof and used in a very recent study of noisy circadian rhythms.⁵ This correlation time is given in the weak-noise limit by

$$\tau = \frac{T^3}{2\pi^2 |\partial T / \partial E|} \Omega + \mathcal{O}(\Omega^0), \quad (84)$$

where Ω is the extensivity parameter which is proportional to the number of molecules in the system and $\partial T / \partial E$ is the derivative of the period T of the cycle with respect to the pseudoenergy of the Hamilton–Jacobi equation associated with the chemical master equation. The proof of the formula (84) is based on the Hamilton–Jacobi method and, especially, on the Legendre transform described in Sec. III B, which is at the origin of the derivative of the period with respect to the pseudoenergy.

We have moreover obtained an expression given by Eq. (59) for the autocorrelation function of a noisy limit cycle and which uses the Fourier expansion of the macroscopic limit cycle of the noiseless system. This expression takes into account the phase diffusion induced by the fluctuations in the weak-noise limit.

Formula (84) allows us to estimate the minimum number of molecules that is required in order for a nonequilibrium

chemical system to sustain correlated oscillations and to act as a chemical clock. This fundamental lower limit is imposed by the molecular fluctuations. For a typical chemical oscillator based on the reaction scheme of the Brusselator or the models of circadian rhythms studied in Refs. 2–5, this minimum number is of the order of 10 to 100 molecules distributed among the chemical species involved in the reaction. It is remarkable that the fundamental lower limit for correlated nonequilibrium oscillations essentially corresponds to nanometric systems. For such small systems, the oscillations may still persist but the molecular fluctuations are so large that the oscillations become extremely irregular in time as illustrated in Fig. 2(a). In such an extremely noisy case, the period of oscillations is no longer well defined so that such an ultras-small system can no longer be considered as a chemical clock. The present estimation of the minimum number of molecules suggests that chemical clocks based on a kinetic network of reactions can exist from the nanoscale up to the macroscale. The lower limit for sustained and correlated oscillations is thus surprisingly close to the molecular scale.

On the nanoscale itself, we can consider another kind of mesoscopic nonequilibrium systems which are the biomolecular motors.^{40,41} These systems are functioning thanks to a specific molecular architecture. Here also, irregularity arises in the motion of the motors because of molecular noise. This molecular noise can be expected to induce a phase diffusion in the rotation of the motor with respect to its average angular motion. As a consequence, a correlation time can be defined for the irregular rotation of the shaft of the motor. The stronger the stochastic fluctuations on the motor rotation, the shorter the correlation time. Albeit the clocks described in the present paper are purely chemical, the biomolecular motors are mechanochemical, which requires a different description. Nevertheless, the stochastic motion of biomolecular motors are also described by Fokker–Planck-type equations for the probabilities that the biomolecular complex be in different conformations determined, in particular, by the rotational angle and the kinetic states.^{40,41} In this perspective, the analysis developed in the present paper could be extended to these nanometric systems as well.

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