

H-Theorem for Lifetime Distributions of Active Intermediates in Nonequilibrium Chemical Systems with Stable Limit Cycles

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Received: October 17, 1997

The large time behavior of the lifetime distributions of active intermediates is investigated for nonequilibrium chemical systems with stable limit cycles. The lifetime distributions are the solutions of a system of partial differential equations which can be integrated by using the method of characteristics. A generalized *H*-function is defined in terms of two sets of solutions of these partial differential equations corresponding to two different initial solutions. An *H*-theorem is proven which shows that for a system with a stable limit cycle all transient lifetime distributions evolve toward the same normal form which is a periodic function of time and which, up to a constant phase factor, is independent of the initial conditions. A frequency response tracer experiment is suggested for the evaluation of the probability distribution of the lifetime of an intermediate. A special experiment makes possible the direct measurement of the Fourier transform of the probability distribution with respect to the lifetime of a molecule. This Fourier transform is a generalized susceptibility function which depends both on time and frequency. The real and imaginary parts for the susceptibility function are related to each other by means of a set of generalized Kramers–Kronig relationships, which are a consequence of causality. The theory is used for generalizing the kinetic spectrum analysis of time-dependent normal processes. An alternative approach to spectral kinetic analysis determines the influence of environmental fluctuations on the lifetime distributions. It is shown that the average lifetimes of active intermediates in the system increase with the strength of environmental fluctuations and in the limit of random processes with long memory, even though the concentrations remain finite, the average lifetimes tend to infinity. A numerical computation of the large time behavior of active intermediates is carried out in the particular case of the Selkov model with a stable limit cycle. The numerical analysis confirms the theoretical predictions presented in the article.

1. Introduction

In chemical kinetics the life time of an active intermediate is an important variable which characterizes the time scale of the process in which the intermediate is involved. In the literature different techniques have been suggested for the direct experimental evaluation of this parameter; they are used extensively for the analysis of chain reactions,¹ such as radical polymerization.² These techniques are generally based on the assumption that the mean life time of an active intermediate X_i can be evaluated as the ratio between its concentration x_i and its rate of disappearance W_i^- :

$$\langle \tau \rangle_{x_i} = x_i / W_i^- \quad (1)$$

Unfortunately eq 1 is valid only for the particular case of stationary processes for which both x_i and W_i^- are time-independent. For a time-dependent process eq 1 is not valid anymore. An alternative theory has been suggested for the study of time dependent systems, based on the use of age-dependent balance equations.³ If the kinetics of a reaction system is known, this theory provides analytical expressions for the

probability distributions of the lifetime of the different individuals in the system. For nonstationary chemical systems with unknown kinetics the theory has suggested that a succession of tracer measurements makes possible the experimental evaluation of the distribution functions.³ For one-variable systems a connection has been made between this formalism and the thermodynamic description of nonequilibrium systems.⁴

The above mentioned time-dependent approach to the problem of lifetime distributions has been developed for transient processes approaching a steady state. The purpose of this article is to develop a more general theory for the case when the chemical system investigated evolves toward a time-dependent attractor, for example, a stable limit cycle. For such systems the theoretical approach must be different from the one suggested for the evolution toward a steady state because in this case it is not clear whether in the long run the system forgets its past or not. We intend to check whether in the long run the distribution of the life time of different molecular species tends toward a normal form independent of the initial conditions. For accomplishing this task we combine the method of age-dependent balance equations with the method of H-(Lyapunov) functions.

2. Formulation of the Problem

We consider an open isothermal system made up of many active intermediates X_i , $i = 1, 2, \dots$, as well as many stable

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species A_i , $i = 1, 2, \dots$, and assume that the concentrations a_i , $i = 1, 2, \dots$ of the stable species are kept constant by exchange of matter with large reservoirs connected to the system by membranes permeable only to A_i , $i = 1, 2, \dots$. The deterministic evolution equations for the concentrations x_i , $i = 1, 2, \dots$ of the active intermediates X_i , $i = 1, 2, \dots$ are given by

$$dx_i(t)/dt = W_i^+(\mathbf{x}(t)) - W_i^-(\mathbf{x}(t)), \quad i = 1, 2, \dots \quad (2)$$

where $W_i^\pm(\mathbf{x})$, $i = 1, 2, \dots$ are the rates of generation and consumption of the different intermediates, respectively. We assume that these rates depend on the composition vector of the active intermediates $\mathbf{x}(t) = (x_1(t), x_2(t), \dots)$ but are independent of time. We consider that in the long run all solutions of the kinetic eq 2 tend toward a family of normal solutions $\mathbf{x}^*(t)$. All normal solutions from this family have the same shape, and up to a time independent phase factor, are equal to each other and correspond to the same stable limit cycle:

$$\lim_{t \rightarrow \infty} \mathbf{x}(t; \mathbf{x}(t_0)) = \mathbf{x}^*(t) \quad (3)$$

We denote by $\eta_i(\tau; t)d\tau$ the density of particles of type X_i at time t with a lifetime in the system between τ and $\tau + d\tau$. We have

$$\int_0^\infty \eta_i(\tau; t)d\tau = x_i(t) \quad (4)$$

For evaluating these density functions we notice that

$$\lambda_i^-(t)dt = [W_i^-(\mathbf{x}(t))/x_i(t)]dt \quad (5)$$

is the probability that a particle X_i disappears in a time interval $t, t + dt$. By taking eq 5 into account we can derive the following balance equations for $\eta_i(\tau; t)d\tau$:

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau} \right) \eta_i(\tau; t) = - \left[\frac{W_i^-(\mathbf{x}(t))}{x_i(t)} \right] \eta_i(\tau; t), \quad i = 1, 2, \dots \quad (6)$$

$$\eta_i(\tau = 0; t) = W_i^+(\mathbf{x}(t)), \quad i = 1, 2, \dots \quad (7)$$

We denote by

$$\xi_i(\tau; t)d\tau \quad \text{with} \quad \int_0^\infty \xi_i(\tau; t)d\tau = 1 \quad (8)$$

the distribution of active intermediates X_i at time t with respect to their transit times. This distribution can be expressed in terms of the density function $\eta_i(\tau; t)d\tau$ as

$$\xi_i(\tau; t)d\tau = \frac{\eta_i(\tau; t)d\tau}{\int_0^\infty \eta_i(\tau; t)d\tau} = \frac{\eta_i(\tau; t)d\tau}{x_i(t)} \quad (9)$$

By expressing in eqs 6 and 7 the density functions $\eta_i(\tau; t)d\tau$ in terms of $\xi_i(\tau; t)$ and $x_i(t)$ and eliminating $dx_i(t)/dt$ from eq 2, we can derive a system of evolution equations for the lifetime distributions $\xi_i(\tau; t)d\tau$:

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau} \right) \xi_i(\tau; t) = -\lambda_i^+(\tau) \xi_i(\tau; t), \quad i = 1, 2, \dots \quad (10)$$

$$\xi_i(\tau = 0; t) = \lambda_i^+(t), \quad i = 1, 2, \dots \quad (11)$$

where

$$\lambda_i^+(t)dt = [W_i^+(\mathbf{x}(t))/x_i(t)]dt \quad (12)$$

is the infinitesimal probability that a new X_i intermediate is generated at a time between t and $t + dt$.

A formal analytical solution of eqs 10 and 11 can be derived by using the method of characteristics. The solutions corresponding to the following initial conditions:

$$\xi_i(\tau; t = t_0) = \xi_i^0(\tau), \quad i = 1, 2, \dots \quad (13)$$

are given by

$$\begin{aligned} \xi_i(\tau; t) = & h(t - t_0 - \tau) \lambda_i^+(t - \tau) \exp[-\int_{t-\tau}^t \lambda_i^+(t')dt'] + \\ & h(\tau - t + t_0) \xi_i^0(\tau - t + t_0) \exp[-\int_{t_0}^t \lambda_i^+(t')dt'], \end{aligned} \quad i = 1, 2 \quad (14)$$

where $h(x)$ is Heaviside's step function. The moments of the mean lifetime can be easily computed from eq 14, resulting in

$$\begin{aligned} \langle \tau^m(t) \rangle_i = & \int_0^\infty \tau^m \xi_i(\tau; t) d\tau = \\ & \sum_{k=0}^{m-1} \frac{m!}{k!(m-k)!} \langle \tau^{m-k}(t_0) \rangle_i (t - t_0)^k \exp[-\int_{t_0}^t \lambda_i^+(t')dt'] + \\ & m \int_{t_0}^t (t - t')^{m-1} \exp[-\int_{t'}^t \lambda_i^+(t')dt'] dt', \quad i = 1, 2, \dots; \\ & m = 1, 2, \dots \end{aligned} \quad (15)$$

We are interested in the study of the large time behavior of the lifetime distributions. Formally the large time behavior can be investigated by pushing the initial conditions to minus infinity, to $t_0 \rightarrow -\infty$. The structure of eqs 14 and 15 suggests that in this limit the terms depending on the initial distributions vanish and that, up to a constant phase factor, we should have

$$\lim_{t_0 \rightarrow -\infty} \xi_i(\tau; t) = \xi_i^*(\tau; t) = \lambda_i^+(t - \tau) \exp[-\int_{t-\tau}^t \lambda_i^+(t')dt'] \quad (16)$$

$$\begin{aligned} \lim_{t_0 \rightarrow -\infty} \langle \tau^m(t) \rangle_i = & \langle \tau^m(t) \rangle_i^* = \\ & m \int_{-\infty}^t (t - t')^{m-1} \exp[-\int_{t'}^t \lambda_i^+(t')dt'] dt' \\ & \text{independent of} \quad \langle \tau^u(t) \rangle_i, \quad u = 1, \dots, m \end{aligned} \quad (17)$$

3. H-Theorem for Stable Limit Cycles

To prove the validity of the conjecture expressed by eqs 16 and 17, we generalize the method of H-functions for age- and time-dependent solutions. To achieve that we combine a technique suggested by Vlad and Ross⁵ for age-dependent master equations with a method suggested by Brey and Prados⁶ for stochastic master equations with time-dependent coefficients.⁶ We consider two different sets of solutions of the evolution eqs 10 and 11, $\xi_i^{(1)}(\tau; t)$ and $\xi_i^{(2)}(\tau; t)$, $i = 1, 2, \dots$, corresponding to two sets of different initial conditions, $\xi_i^{(1)}(\tau; t_0)$ and $\xi_i^{(2)}(\tau; t_0)$, ($i = 1, 2, \dots$, and construct the functions

$$H_i(t) = \int_0^\infty \xi_i^{(1)}(\tau; t) \ln \left[\frac{\xi_i^{(1)}(\tau; t)}{\xi_i^{(2)}(\tau; t)} \right] d\tau \quad (18)$$

which are functionals of the two sets of solutions, ($\xi_i^{(1)}(\tau; t)$ and $\xi_i^{(2)}(\tau; t)$, $i = 1, 2, \dots$. The next step of our approach is to show that the functions defined by eqs 18 fulfill the constraints typical for an H-function, that is

$$H_i(t) > 0 \quad \text{for} \quad \xi_i^{(1)}(\tau; t) \neq \xi_i^{(2)}(\tau; t) \quad \text{and} \\ H_i(t) = 0 \quad \text{for} \quad \xi_i^{(1)}(\tau; t) = \xi_i^{(2)}(\tau; t) \quad (19)$$

$$\dot{H}_i(t) < 0 \quad \text{for} \quad \xi_i^{(1)}(\tau; t) \neq \xi_i^{(2)}(\tau; t) \quad \text{and} \\ \dot{H}_i(t) = 0 \quad \text{for} \quad \xi_i^{(1)}(\tau; t) = \xi_i^{(2)}(\tau; t) \quad (20)$$

The proof of eq 19 is based on the well-known inequality

$$x \ln x + 1 - x > 0 \quad \text{for} \quad x > 0, x \neq 1 \quad \text{and} \\ x \ln x + 1 - x = 0 \quad \text{for} \quad x = 1 \quad (21)$$

By integrating eq 10 term by term over the lifetime, from $\tau = 0$ to $\tau = \infty$, and by making use of eq 11, we come to

$$\frac{\partial}{\partial t} \int_0^\infty \xi_i(\tau; t) d\tau = 0 \quad (22)$$

It follows that the evolution equations 10–11 conserve the normalization condition of the lifetime distributions. In particular, if the initial lifetime distributions are normalized to unity, the same is true for the distributions at later times:

$$\text{if} \quad \int_0^\infty \xi_i(\tau; t) d\tau = 1 \quad \text{then} \quad \int_0^\infty \xi_i(\tau; t) d\tau = 1 \quad (23)$$

By making use of eq 23, eq 18 can be rewritten as

$$H_i(t) = \int_0^\infty \left\{ \xi_i^{(1)}(\tau; t) \ln \left[\frac{\xi_i^{(1)}(\tau; t)}{\xi_i^{(2)}(\tau; t)} \right] - \xi_i^{(1)}(\tau; t) + \xi_i^{(2)}(\tau; t) \right\} d\tau \quad (24)$$

from which, by taking the inequality 21 into account we come to eq 19.

The derivation of eq 20 is a little bit more complicated. By differentiating eq 18 term by term with respect to the time variable, we obtain

$$\dot{H}_i(t) = \int_0^\infty \left\{ \frac{\partial}{\partial \tau} \left[\frac{\xi_i^{(1)}(\tau; t)}{\xi_i^{(2)}(\tau; t)} \right] \right\} d\tau - \int_0^\infty \left\{ \left[\frac{\xi_i^{(1)}(\tau; t)}{\xi_i^{(2)}(\tau; t)} \right] \frac{\partial}{\partial \tau} [\xi_i^{(2)}(\tau; t)] \right\} d\tau \quad (25)$$

Now we express the time derivatives of the two distribution functions $\xi_i^{(1)}(\tau; t)$ and $\xi_i^{(2)}(\tau; t)$ $i = 1, 2, \dots$ in terms of the corresponding derivatives with respect to the lifetime. From eq 10 we obtain

$$\frac{\partial}{\partial \tau} [\xi_i^{(1;2)}(\tau; t)] = -\frac{\partial}{\partial \tau} [\xi_i^{(1)}(\tau; t)] - \lambda_i^+(t) \xi_i^{(1;2)}(\tau; t) \quad (26)$$

and then eq 25 can be rewritten as

$$\dot{H}_i(t) = -\lambda_i^+(t) \int_0^\infty \xi_i^{(1)}(\tau; t) \left\{ \ln \left[\frac{\xi_i^{(1)}(\tau; t)}{\xi_i^{(2)}(\tau; t)} \right] - 1 \right\} d\tau - \int_0^\infty \left\{ \frac{\partial}{\partial \tau} [\xi_i^{(1)}(\tau; t)] \ln \left[\frac{\xi_i^{(1)}(\tau; t)}{\xi_i^{(2)}(\tau; t)} \right] \right\} d\tau + \int_0^\infty \left\{ \left[\frac{\xi_i^{(1)}(\tau; t)}{\xi_i^{(2)}(\tau; t)} \right] \frac{\partial}{\partial \tau} [\xi_i^{(2)}(\tau; t)] \right\} d\tau \quad (27)$$

In eq 27 the integrals depending on the derivatives of the

distribution functions with respect to the lifetime can be transformed by means of partial integrations. In order that the integrals in eq 23 be convergent, we should have

$$\lim_{\tau \rightarrow \infty} \xi_i^{(1;2)}(\tau; t) = 0 \quad (28)$$

The values of the distribution functions corresponding to a lifetime equal to zero can be computed from eq 11 as follows:

$$\xi_i^{(1;2)}(\tau = 0; t) = \lambda_i^+(t) \quad (29)$$

By performing the partial integrations in eq 27 and making use of the boundary values (eqs 28 and 29) and after some calculations, we obtain

$$\dot{H}_i(t) = -\lambda_i^+(t) \int_0^\infty \xi_i^{(1)}(\tau; t) \left\{ \ln \left[\frac{\xi_i^{(1)}(\tau; t) \xi_i^{(2)}(0; t)}{\xi_i^{(1)}(0; t) \xi_i^{(2)}(\tau; t)} \right] \right\} d\tau \quad (30)$$

Now we use the inequality

$$\ln x + 1 - x < 0 \quad \text{for} \quad x > 0, x \neq 1 \quad \text{and} \\ \ln x + 1 - x = 0 \quad \text{for} \quad x = 1 \quad (31)$$

By combining eq 30 and 31 and making use of the conditions in eq 23 for the conservation of normalization after some calculations we obtain eq 20.

From the above derivations it follows that the functions defined by eq 18 are H -functions for the evolution eqs 10–11. It follows that in the long run the two sets of distribution functions in terms of which the H -functions are defined, $\xi_i^{(1)}(\tau; t)$ and $\xi_i^{(2)}(\tau; t)$, $i = 1, 2, \dots$ tend to have a common shape, that is, up to a phase difference $\Delta\varphi_i$:

$$\lim_{t_0 \rightarrow -\infty} \xi_i^{(1)}(\tau; t) = \lim_{t_0 \rightarrow -\infty} \xi_i^{(2)}(\tau; t - \Delta\varphi_i) = \xi_i^{*(1)}(\tau; t) = \xi_i^{*(2)}(\tau; t - \Delta\varphi_i) = \xi_i^*(\tau; t) \quad (32)$$

In this equation the limit form $\xi_i^*(\tau; t)$ of the lifetime distributions is the one given by the formal representations 14 of the solutions of the evolution equations, that is, by eq 16.

We draw attention to a special feature of the systems with a stable limit cycle. Strictly speaking for a stable limit cycle the normal solutions $\xi_i^*(\tau; t)$ of the kinetic eq 2 of the homogeneous system may be different for different initial conditions. However, their shape is identical and independent of the initial conditions, that is, they are the same up to a time-independent phase difference and all correspond to the same limit cycle. Given two normal solutions $\xi_i^{*(1)}(\tau; t)$ and $\xi_i^{*(2)}(\tau; t)$, the solutions $\xi_i^{*(1)}(\tau; t)$ can be obtained from $\xi_i^{*(2)}(\tau; t)$ and vice versa by changing the origin of the time axis. The two solutions are characterized by the same amplitude factors and the difference between their phases $\Delta\varphi_i$ is independent of time.

For a stationary regime the mean life time of an intermediate given by eq 1 is a characteristic time scale of the chemical process investigated. For a stable limit cycle, however, the corresponding average value, determined from eq 17 for $m = 1$,

$$\langle \tau(t) \rangle_i^* = \int_{-\infty}^t \exp[-\int_{t'}^t \lambda_i^+(t') dt'] dt'' \quad (33)$$

is a periodic function of time rather than a constant number. A suitable number characterizing the time scale of the process is the time average of the asymptotic mean lifetime given by eq 33:

$$\langle \tau \rangle_i^* = \frac{1}{T} \int_{-T/2}^{+T/2} \langle \tau(t+x) \rangle_i^* dx = \frac{1}{T} \int_{-T/2}^{+T/2} \int_{-\infty}^{t+x} \exp[-\int_{t'}^{t+x} \lambda_i^+(t') dt'] dt'' dx \quad (34)$$

where T is the period of oscillation corresponding to the limit cycle. An analytic estimate of the time average can be given by using the technique of harmonic linearization. We expand the generation rate $\lambda_i^+(t)$ in a Fourier series and neglect the superior harmonics as follows:

$$\lambda_i^+(t') \approx \overline{\lambda_i^+} + A_i^{(1)} \sin\left[\frac{2\pi t}{T} + \vartheta_i\right] \quad (35)$$

where

$$\overline{\lambda_i^+} = \frac{1}{T} \int_{-T/2}^{+T/2} \lambda_i^+(t+x) dx \quad (36)$$

is the temporal average of the generation rate $\lambda_i^+(t)$ and

$$A_i^{(1)} = \frac{2}{T} \left\{ \left[\int_{-T/2}^{+T/2} \sin\left[\frac{2\pi(t+x)}{T}\right] \lambda_i^+(t+x) dx \right]^2 + \left[\int_{-T/2}^{+T/2} \cos\left[\frac{2\pi(t+x)}{T}\right] \lambda_i^+(t+x) dx \right]^2 \right\}^{1/2} \quad (37)$$

$$\vartheta_i = \arctan \left\{ \frac{\left[\int_{-T/2}^{+T/2} \cos\left[\frac{2\pi(t+x)}{T}\right] \lambda_i^+(t+x) dx \right]}{\left[\int_{-T/2}^{+T/2} \sin\left[\frac{2\pi(t+x)}{T}\right] \lambda_i^+(t+x) dx \right]} \right\} \quad (38)$$

are the total amplitude and the phase of the first harmonic of $\lambda_i^+(t)$, respectively. By using the approximation 35 in the limit to $t_0 \rightarrow -\infty$, the integrals in eq 34 can be expressed in terms of modified Bessel functions. We have

$$\langle \tau \rangle_i^* = \frac{[I_0(A_i^{(1)})]^2}{\overline{\lambda_i^+}} \quad (39)$$

where $I_0(x)$ is the modified Bessel function of order zero.

4. Proposed Experiment

For systems evolving toward a steady state, a succession of tracer experiments has been suggested,³ which makes possible, at least in principle, the measurement of the lifetime distributions of the different reaction intermediates. The method consists in recording the response of the system to different pulses of labeled chemicals introduced in the system at different times. For a chemical system with a stable limit cycle, however, such an approach is not appropriate because the dynamical behavior of the system is more complicated. Here we suggest a different type of experiment, based on the use of frequency response. We consider that the chemical process studied takes place in an isothermal continuous stirred tank reactor (CSTR) operated with a constant total flow rate and with constant input concentrations. We assume that at least one of the chemicals entering the system is available in two different forms, unlabeled and labeled, respectively, and that the kinetic isotope effect can be neglected (i.e., the kinetic parameters are the same both for the labeled and unlabeled compounds). Although the total input concentrations of chemicals are kept constant, we assume that it is possible to control the proportion of labeled compounds entering the systems. Under these circumstances the overall kinetic behavior of the system, expressed in terms of total

concentrations, is not affected by the introduction of tracer in the system. Only the proportions of labeled compounds in the reactor depend on the amounts of tracers introduced in the system. By measuring the concentrations of labeled chemicals in the reactor it is possible to evaluate the distributions of lifetimes of different individuals.

For a given reaction intermediate, which may exist in an unlabeled form X_i as well as in a labeled form, $X_i^{\#}$, we assume that it is possible to measure the time dependence of the following fractions: 1. The ratio $\beta_i(t)$ between the rate $W_i^{\#}[\mathbf{x}^*(t)]$ of generation of the labeled compound $X_i^{\#}$ and the total rate of generation $W_i^+[\mathbf{x}^*(t)]$ of the two forms, X_i and $X_i^{\#}$, labeled and unlabeled,

$$\beta_i(t) = W_i^{\#}[\mathbf{x}^*(t)]/W_i^+[\mathbf{x}^*(t)] \quad (40)$$

2. The proportion $\alpha_i(t)$ of the active intermediate $X_i^{\#}$:

$$\alpha_i(t) = x_i^{\#}(t)/x_i^*(t) \quad (41)$$

where $x_i^{\#}(t)$ and $x_i^*(t)$ are the concentrations of the labeled active intermediate and the total concentration of the active intermediate, labeled and unlabeled, corresponding to the limit cycle.

In order to extract the information about the lifetime distributions from these two functions, $\alpha_i(t)$ and $\beta_i(t)$ we must derive an evolution equation for the concentration $x_i^{\#}(t)$ of labeled intermediate in the system. To do so we apply the method of Neiman and Gal,⁷ resulting in

$$\frac{d}{dt} x_i^{\#}(t) = W_i^+[\mathbf{x}^*(t)] - W_i^-[\mathbf{x}^*(t)] \frac{x_i^{\#}(t)}{x_i^*(t)} \quad (42)$$

Equation 42 must be supplemented by the kinetic eq 2, applied for the limit cycle $\mathbf{x}(t) = \mathbf{x}^*(t)$:

$$\frac{d}{dt} x_i^*(t) = W_i^+[\mathbf{x}^*(t)] - W_i^-[\mathbf{x}^*(t)] \quad (43)$$

By combining eqs 40–43 we can derive the following relationship between $\alpha_i(t)$ and $\beta_i(t)$

$$\frac{d}{dt} \alpha_i(t) + \alpha_i(t) \frac{W_i^+[\mathbf{x}^*(t)]}{x_i^*(t)} = \beta_i(t) \frac{W_i^+[\mathbf{x}^*(t)]}{x_i^*(t)} \quad (44)$$

This is a differential equation in $\alpha_i(t)$. Although in the general case its solution depends on the initial value $\alpha_i(t_0)$ in the limit $t_0 \rightarrow -\infty$, its contribution decreases exponentially to zero. We have

$$\begin{aligned} \alpha_i(t) &= \lim_{t_0 \rightarrow -\infty} \left\{ \exp \left[- \int_{t_0}^t \frac{W_i^+[\mathbf{x}^*(t')]}{x_i^*(t')} dt' \right] \alpha_i(t_0) + \right. \\ &\quad \left. \int_0^{t-t_0} \frac{W_i^+[\mathbf{x}^*(t-x)]}{x_i^*(t-x)} \exp \left[- \int_{t-x}^t \frac{W_i^+[\mathbf{x}^*(t')]}{x_i^*(t')} dt' \right] \beta_i(t-x) dx \right\} \\ &= \int_0^\infty \lambda_i^+(t-x) \exp \left[- \int_{t-x}^t \lambda_i^+(t') dt' \right] \beta_i(t-x) dx \quad (45) \end{aligned}$$

Now the relationship between the response experiment and the distribution of lifetimes is obvious. From eqs 17 and 45 we notice that the response function $\alpha_i(t)$ is given by the convolution product between the excitation function $\beta_i(t)$ and the normal form $\xi_i^*(\tau; t)$ of the lifetime distribution corresponding to the limit cycle:

$$\alpha_i(t) = \int_0^\infty \xi_i^*(\tau; t) \beta_i(t - \tau) d\tau \quad (46)$$

For a typical frequency response experiment the excitation function $\beta_i(t)$ is a periodic function characterized by a single harmonic:

$$\beta_i(t) = \bar{\beta}_i + \Delta\beta_i \exp(j\omega t) \quad (47)$$

where ω is a characteristic frequency, and $\bar{\beta}_i$ and $\Delta\beta_i$ are the temporal average and the amplitude of the excitation function, respectively. By combining eqs 46 and 47 come to

$$\alpha_i(t) = \bar{\beta}_i + \Xi_i^*(\omega; t) \Delta\beta_i \exp(j\omega t) \quad (48)$$

where

$$\Xi_i^*(\omega; t) = \int_0^\infty \xi_i^*(\tau; t) \exp(-j\omega\tau) d\tau \quad (49)$$

is a susceptibility function given by the one-sided Fourier transform of the normal form of the lifetime distribution, $\xi_i^*(\tau; t)$. The frequency response of the system, expressed by eq 48, is rather complicated: it is made up of the superposition of two different oscillatory processes, an external oscillation given by the excitation (eq 47) and an internal oscillation, represented by the complex susceptibility $\Xi_i^*(\omega; t)$, which, like the normal distribution $\xi_i^*(\tau; t)$, is a periodic function of time. The interaction between these two oscillations may lead to interesting effects, which can be studied by using eq 48. We do not intend to deal with this problem here. The main implication of eq 48 considered in this article is the possibility of evaluating the time and frequency dependence of the susceptibility function $\Xi_i^*(\omega; t)$ from a set of frequency response experiments corresponding to different input frequencies. If the experimental data are accurate then, from the susceptibility function $\Xi_i^*(\omega; t)$, it is possible to evaluate the normal distribution function of the lifetime, $\xi_i^*(\tau; t)$ by means of numerical inverse Fourier transformation. If the experimental data are not very accurate, then it is still possible to evaluate the first two or three moments and cumulants of the lifetime. Since the mean lifetime of an intermediate is nonnegative, it follows that

$$\xi_i^*(\tau < 0; t) = 0 \quad (50)$$

and thus the characteristic function of the probability distribution $\xi_i^*(\tau; t)$ is identical with the susceptibility function $\Xi_i^*(\omega; t)$ which is experimentally accessible. It follows that the moments $\langle \tau^m(t) \rangle_i^*$, $m = 1, 2, \dots$ and the cumulants $\langle\langle \tau^m(t) \rangle\rangle_i^*$, $m = 1, 2, \dots$ of the lifetime can be evaluated by computing the derivatives of $\Xi_i^*(\omega; t)$ and $\ln \Xi_i^*(\omega; t)$ for zero frequency, respectively, as follows:

$$\langle \tau^m(t) \rangle_i^* = j^m \frac{d^m}{d\omega^m} \Xi_i^*(\omega = 0; t), \quad m = 1, 2, \dots \quad (51)$$

$$\langle\langle \tau^m(t) \rangle\rangle_i^* = j^m \frac{d^m}{d\omega^m} \ln \Xi_i^*(\omega = 0; t), \quad m = 1, 2, \dots \quad (52)$$

5. Generalized Kramers–Kronig Relations

We notice a formal analogy between the description of the tracer experiments suggested in this article and the linear response theory⁸ of Kubo for nonequilibrium systems with memory. From this point of view eq 46 and its particular case (eq 48) corresponding to a frequency response experiment, are the analogs of the force–flux relationships for systems with

memory. This analogy is only superficial because Kubo's theory is limited to linear systems, whereas the underlying dynamics of the chemical processes studied in this article is nonlinear. The linear structure of eqs 46 and 48 is generated by the particular experiment suggested in this article (i.e., the fact that the total influx concentrations are kept constant and only the proportion of tracer molecules is variable). If the total influx concentrations are not kept constant, the linear relationships 46 and 48 do not hold anymore. Even when the total influx concentrations are constant, and eqs 46 and 48 are valid, the underlying nonlinear dynamics of the process generates some features which are missing from the linear systems described by the Kubo's theory. The susceptibility function is $\Xi_i^*(\omega; t)$ given by a Fourier transform with respect to the lifetime of a molecule and not with respect to the time variable. For this reason, unlike in the case of Kubo's theory, in our approach the susceptibility function $\Xi_i^*(\omega; t)$ depends both on frequency and on time. For a system with a limit cycle the time dependence is periodic and determined by the nonlinear underlying dynamics of the process.

Despite the fact that the susceptibility function $\Xi_i^*(\omega; t)$ is both frequency- and time-dependent, some general features of Kubo's theory are preserved in the case of our approach. An important consequence is generated by the causality principle which leads to a general relationship of the Kramers–Kronig type^{8–10} between the real and imaginary parts of the susceptibility function. We express $\Xi_i^*(\omega; t)$ in the form

$$\Xi_i^*(\omega; t) = \chi_i'(\omega; t) - j\chi_i''(\omega; t) \quad (53)$$

where $\chi_i'(\omega; t)$ and $\chi_i''(\omega; t)$ are the real and imaginary contributions to $\Xi_i^*(\omega; t)$, respectively. The relationships between $\chi_i'(\omega; t)$ are given below and have the form

$$\chi_i'(\omega; t) = -\frac{1}{\pi} \int_{-\infty}^{+\infty} d\omega' \frac{\mathcal{R}}{\omega' - \omega} \chi_i''(\omega'; t) \quad (54)$$

$$\chi_i''(\omega; t) = -\frac{1}{\pi} \int_{-\infty}^{+\infty} d\omega' \frac{\mathcal{R}}{\omega' - \omega} \chi_i'(\omega'; t) \quad (55)$$

where the notation \mathcal{R} indicates the Cauchy principal value. These relationships can be derived in the same way as the classical Kramers–Kronig relationships for time-independent complex susceptibility functions.^{9,10} To save space the detailed derivation is not given here. The main idea is to introduce the complex function

$$\Sigma_i^*(z) = \int_0^\infty \xi_i^*(\tau; t) \exp(jz\tau) d\tau \quad (56)$$

(where z is a complex frequency variable) and to investigate the influence of the causality on the analytic properties of this function. The function is related to the susceptibility by means of the relation

$$\Xi_i^*(\omega; t) = \lim_{\epsilon \rightarrow +0} \Sigma_i^*(z = -\omega + j\epsilon) =$$

$$\lim_{\epsilon \rightarrow +0} \int_0^\infty \xi_i^*(\tau; t) \exp(-(j\omega + \epsilon)\tau) d\tau \quad (57)$$

Since in eq 56 the integral is taken from zero to infinity, the function $\xi_i^*(z)$ is analytic in the upper z -plane. This analyticity property is a consequence of the causality principle which requires that the lifetime of a molecule is never negative (see also eq 50). The analytic behavior of the function $\xi_i^*(z)$ in the

upper z -plane makes it possible to express it by a closed path integral of the Cauchy type. By separating the real and imaginary parts in this Cauchy integral and using eqs 53 and 57, we obtain the generalized Kramers–Kronig relationships 54 and 55.

6. Kinetic Spectrum Analysis and Normal Lifetime Distributions

For a stationary state the distribution of the lifetime of an active intermediate is exponential

$$\xi_i^{*(st)}(\tau) = \Omega_i^{*(st)} \exp(-\tau \Omega_i^{*(st)}) \quad (58)$$

where the characteristic frequency $\Omega_i^{*(st)}$ is the reciprocal value of the average lifetime $\langle \tau \rangle_{x_i}$, expressed by eq 1:

$$\Omega_i^{*(st)} = 1/\langle \tau \rangle_{x_i} = W_i^-/x_i \quad (59)$$

The exponential distribution (eq 58) is intimately related to the Poissonian behavior of the statistics of reaction events at a stationary state. For a time-dependent normal regime, however, the statistics of the reaction events is generally non-Poissonian, resulting in a nonexponential distribution of the lifetime. The violation of Poissonian statistics and of its exponential correspondent for the lifetime is of considerable theoretical interest. In order to measure the degree of violation of the exponential distribution of the lifetime, we introduce as a reference distribution a time-dependent analogue of the exponential law (eq 58):

$$\xi_i^{*(ref)}(t; \tau) = \Omega_i^*(t) \exp[-\tau \Omega_i^*(t)] \quad (60)$$

where $\Omega_i^*(t)$ is a time-dependent characteristic frequency given by the reciprocal value of the average lifetime $\langle \tau(t) \rangle_i^*$ for the normal regime

$$\Omega_i^*(t) = 1/\langle \tau(t) \rangle_i^* \quad (61)$$

In the case of the reference distribution (eq 60) the complex susceptibility function $\Xi_i^*(\omega; t)$, its real and imaginary components, $\chi_i'(\omega; t)$ and $\chi_i''(\omega; t)$, as well as the moments, $\langle \tau^m(t) \rangle_i^{*(ref)}$, $m = 1, 2, \dots$ and the cumulants $\langle \langle \tau^m(t) \rangle \rangle_i^{*(ref)}$, $m = 1, 2, \dots$ of the lifetime can be evaluated analytically. We obtain

$$\Xi_i^*(\omega; t) = \Omega_i^*(t)/[\Omega_i^*(t) + j\omega] \quad (62)$$

$$\chi_i'(\omega; t) = [\Omega_i^*(t)]^2/[\Omega_i^*(t)^2 + \omega^2] \quad (63)$$

$$\chi_i''(\omega; t) = \omega \Omega_i^*(t)/[\Omega_i^*(t)^2 + \omega^2] \quad (64)$$

and

$$\langle \tau^m(t) \rangle_i^{*(ref)} = m! / [\Omega_i^*(t)]^m = m! [\langle \tau(t) \rangle_i^*]^m, \quad m = 1, 2, \dots \quad (65)$$

$$\langle \langle \tau^m(t) \rangle \rangle_i^{*(ref)} = (m-1)! / [\Omega_i^*(t)]^m = (m-1)! [\langle \tau(t) \rangle_i^*]^m, \quad m = 1, 2, \dots \quad (66)$$

As usual in statistics, we evaluate the distance between the actual normal distribution $\xi_i^*(t; \tau)$ and the reference exponential distribution given by eq 60 by computing the differences between the cumulants attached to the two distributions. As a measure for this distance we introduce the absolute variations

$$\rho_m(t) = \delta \langle \tau^m(t) \rangle_i^* = \langle \tau^m(t) \rangle_i^* - \langle \tau^m(t) \rangle_i^{*(ref)}, \quad m = 2, 3, \dots \quad (67)$$

and the relative variations:

$$\gamma_m(t) = \rho_m(t) / \langle \tau^m(t) \rangle_i^{*(ref)}, \quad m = 2, 3, \dots \quad (68)$$

where $\langle \tau^m(t) \rangle_i^*$ and $\langle \tau^m(t) \rangle_i^{*(ref)}$ are given by eqs 52 and 66, respectively. The evaluation of all these functions $\rho_m(t)$ and $\gamma_m(t)$ is difficult, the difficulty increasing very much with the increase of the index m . In most cases only the functions of order 2, $\rho_2(t)$ and $\gamma_2(t)$, are accessible.

A function related to $\rho_2(t)$ and $\gamma_2(t)$ is the variation of the absolute value of the dispersion of the lifetime:

$$\epsilon(t) = \sqrt{\langle \tau^2(t) \rangle_i^*} - \sqrt{\langle \tau^2(t) \rangle_i^{*(ref)}} = \sqrt{\langle \tau^2(t) \rangle_i^*} - \langle \tau(t) \rangle_i^* \quad (69)$$

The advantage of the function $\epsilon(t)$ is that it can be compared directly with the average lifetime in the normal regime, $\langle \tau(t) \rangle_i^*$. If $\epsilon(t)$ has the same order of magnitude as the average lifetime $\langle \tau(t) \rangle_i^*$ or it is even bigger, $\epsilon(t) \sim \langle \tau(t) \rangle_i^*$ then the normal distribution function $\xi_i^*(t; \tau)$ is very different from the reference exponential distribution $\xi_i^{*(ref)}(t; \tau)$. On the other hand, if the function $\epsilon(t)$ is much smaller than $\langle \tau(t) \rangle_i^*$ and close to zero, $\langle \tau(t) \rangle_i^* \gg \epsilon(t) \sim 0$, then it is likely that the normal distribution $\xi_i^*(t; \tau)$ is close to the reference form $\xi_i^{*(ref)}(t; \tau)$.

Usually in the literature a nonexponential lifetime distribution $\xi(\tau)$ is represented as a superposition of exponentials $\Omega \exp(-\tau \Omega)$, where the frequency Ω is a random variable selected from a certain probability law, $p(\Omega) d\Omega$ with $\int p(\Omega) d\Omega = 1$:

$$\xi(\tau) = \int \Omega \exp(-\tau \Omega) p(\Omega) d\Omega \quad (70)$$

Given an experimental curve, $\xi(\tau)$, it is possible to evaluate the probability $p(\Omega) d\Omega$ of occurrence of different frequencies by solving the integral eqs 70 by means of inverse numerical Laplace transformation. The study of the function $p(\Omega) d\Omega$ reveals interesting features of the processes studied. This approach has been used for the analysis of a large amount of experimental data from various branches of physics and chemistry such as the study of magnetic and dielectric relaxation,¹¹ of protein–ligand interactions,¹² of complex reaction, relaxation and transport processes in disordered systems,¹³ of the kinetic study of complex chemical processes important for the environmental chemistry of aquatic and atmospheric systems,^{14–15} etc. The branch of chemical kinetics dealing with this type of approach is known by the name of “kinetic spectrum analysis”.^{14–17}

In this section we extend the spectral kinetic analysis to the case of time-dependent normal regimes. A very simple approach is the following. We assume that the probability distribution of the different frequencies is time dependent and rewrite eq 70 in the form

$$\xi_i^*(\tau; t) = \int_0^\infty \Omega \exp(-\tau \Omega) p_i(\Omega; t) d\Omega \quad (71)$$

We introduce the survival function of a molecule of age τ :

$$\Phi_i^*(\tau; t) = \int_\tau^\infty \xi_i^*(\tau'; t) d\tau' \quad (72)$$

After some transformations eq 71 can be rewritten as

$$\Phi_i^*(\tau; t) = \int_\tau^\infty \exp(-\tau \Omega) p_i(\Omega; t) d\Omega \quad (73)$$

Equation 73 shows that the probability density of characteristic

frequencies $p_i(\Omega; t)$ is the inverse Laplace transform of the survival function $\Phi_i^*(\tau; t)$ of the lifetime of an intermediate:

$$p_i(\Omega; t) = \mathcal{L}_\tau^{-1} \Phi_i^*(\tau; t) \quad (74)$$

where the operator \mathcal{L}_τ^{-1} denotes the inverse Laplace transformation with respect to the lifetime τ .

By combining eqs 49, 60, and 71 we can derive a set of relationships between the complex susceptibility function $\Xi_i^*(\omega; t)$, its real and imaginary components $\chi_i'(\omega; t)$ and $\chi_i''(\omega; t)$, and the probability density $p_i(\Omega; t)$ of the characteristic frequency Ω . After some integral transformations we come to

$$\Xi_i^*(\omega; t) = \int_0^\infty \frac{\Omega}{\Omega + j\omega} p_i(\Omega; t) d\Omega \quad (75)$$

$$\chi_i'(\omega; t) = \int_0^\infty \frac{\Omega^2}{\Omega^2 + \omega^2} p_i(\Omega; t) d\Omega \quad (76)$$

$$\chi_i''(\omega; t) = \omega \int_0^\infty \frac{\Omega^2}{\Omega^2 + \omega^2} p_i(\Omega; t) d\Omega \quad (77)$$

We notice that the real and complex parts of the susceptibility function can be represented as a superposition of Lorentzian profiles, with a weight function given by $p_i(\Omega; t)$.

Since the characteristic frequency Ω is a nonnegative random variable, the characteristic function of the probability density $p_i(\Omega; t)$ can be defined as a Laplace transform:

$$G_i(\theta; t) = \int_0^\infty \exp(-\theta\Omega) p_i(\Omega; t) d\Omega \quad (78)$$

where θ is the Laplace variable conjugate to the characteristic frequency Ω . By combining eqs 49, 60, 79, and 78, we can derive a relationship between the complex susceptibility function $\Xi_i^*(\omega; t)$, and the characteristic function $G_i(\theta; t)$:

$$\Xi_i^*(\omega; t) = - \int_0^\infty \frac{\partial G_i(\theta; t)}{\partial \theta} \exp(-j\theta\omega) d\theta = 1 - j\omega \int_0^\infty G_i(\theta; t) \exp(-j\theta\omega) d\theta \quad (79)$$

From eq 79 we can express the positive moments $\langle \tau^m(t) \rangle_i^*$, $m = 1, 2, \dots$ and the cumulants $\langle \tau^m(t) \rangle_i^*$, $m = 1, 2, \dots$ of the lifetime in terms of the negative moments of the characteristic frequency Ω , $\langle \Omega^{-m}(t) \rangle_i$, $m = 1, 2, \dots$. By evaluating the derivatives of different orders of $\Xi_i^*(\omega; t)$ and $\ln \Xi_i^*(\omega; t)$ with respect to ω , after lengthy calculations we obtain

$$\langle \tau^m(t) \rangle_i^* = \langle \Omega^{-m}(t) \rangle_i = \sum_{n \leq m} \sum_{\alpha_1, \beta_n} \dots \sum_{\alpha_n, \beta_n} \frac{m!}{\prod \beta_v!} \prod_{v=1}^n \left\{ \frac{\langle \tau^{\alpha_v}(t) \rangle_i^*}{\alpha_v!} \right\}^{\beta_v}, \quad m = 1, 2, \dots \quad (80)$$

$$\sum_v \alpha_v \beta_v = m$$

$$\langle \tau^m(t) \rangle_i^* = \sum_{m_1, m_2, \dots} m! (-1)^{\sum m_v} (\sum m_v - 1)! \prod_v \left[\frac{\langle \Omega^{-v}(t) \rangle_i}{(v!)^{m_v} m_v!} \right]^{m_v}, \quad m = 1, 2, \dots \quad (81)$$

$$\sum v m_v = m$$

where $\sum v m_v = m$ is a partition of the integer m into smaller integers m_1, m_2, \dots

The relationships derived in this section can be used for extracting useful information about the statistical properties of the characteristic frequency from the normal lifetime distribution $\xi_i^*(\tau; t)$ evaluated by numerical integration of the kinetic equations or directly from a tracer experiment. If accurate values for $\xi_i^*(\tau; t)$ are available for any values of the lifetime of a molecule, then it is possible to evaluate the distribution $p_i(\Omega; t)$ and its characteristic function $G_i(\theta; t)$. If the evaluation of $\xi_i^*(\tau; t)$ is not very accurate, then it may still be possible to evaluate the first two or three moments and cumulants of the distribution.

7. Lifetime Distributions and Environmental Fluctuations

The kinetic spectrum analysis displays some strong similarities to the method of Poissonian representation of chemical fluctuations in nonequilibrium statistical mechanics.¹⁸⁻¹⁹ Within the framework of Poissonian representation the probability that at time t the composition vector of the system is equal to $\mathbf{N} = (N_1, N_2, \dots)$ is represented by a superposition of Poissonian distributions:

$$P(\mathbf{N}; t) = \int \dots \int \prod_v \left\{ \frac{(\lambda_v)^{N_v}}{N_v!} \exp(-\lambda_v) \right\} \mathcal{B}(\lambda; t) d\lambda \quad (82)$$

where $\mathcal{B}(\lambda; t) d\lambda$ is a quasiprobability density in the space of Poissonian parameters $\lambda = (\lambda_1, \lambda_2, \dots)$. Equation 82 is similar to eq 71, which expresses the normal lifetime distribution $\xi_i^*(\tau; t)$ as a superposition of exponentials. Both approaches share a limitation. In the case of Poissonian representation, if the probability $P(\mathbf{N}; t)$ of chemical fluctuations is very different from a Poissonian, then it is necessary to use functions $\mathcal{P}(\lambda; t)$ which become negative for some values of the vector $\lambda = (\lambda_1, \lambda_2, \dots)$. This difficulty may be avoided by using the method of analytic continuation.^{18,19} One assumes that the Poissonian parameters $\lambda_1, \lambda_2, \dots$ are complex variables and that the real integrals in eq 82 are replaced by integrals over the complex plane.

The same difficulty occurs in the case of spectral kinetic analysis. If the normal distribution of the lifetime $\xi_i^*(\tau; t)$ is very different from an exponential, then in eq 71 it may be necessary to use functions $p_i(\Omega; t)$ with negative values. This situation can also be dealt with by using the method of analytic continuation and introducing complex characteristic frequencies. This subject is under study and we intend to present the results elsewhere. Here we mention only that the analogy between the technique of Poissonian representation and spectral kinetic analysis is not accidental. It is possible to introduce the Poissonian representation by starting out from spectral kinetic analysis. The study of the relationships between these two approaches is related to that of the connections between the stochastic and deterministic descriptions of chemical systems far from equilibrium.

In this section we suggest an alternative approach to spectral kinetic analysis by using a reference distribution different from the simple exponential shape (eq 60). This alternative makes the spectral kinetic analysis trivial and, on the other hand, makes possible the analysis of the influence of the environmental fluctuations on the lifetime distributions. The main idea of our approach is that the characteristic random frequency Ω should be considered as a random function of time, rather than as a random number. Therefore the statistical properties of Ω can be described in terms of a probability density functional:

$$\mathcal{P}[\Omega(t')] \mathcal{Q}[\Omega(t')] \quad \text{with} \quad \overline{\int \int \mathcal{P}[\Omega(t')] \mathcal{Q}[\Omega(t')] = 1} \quad (83)$$

or by the corresponding characteristic functional:

$$\mathcal{K}[\mathcal{F}(t')] = \overline{\int \int \exp\{-j \int \mathcal{F}(t') \Omega(t') dt'\} \mathcal{P}[\Omega(t')] \mathcal{Q}[\Omega(t')] \quad (84)$$

where $\mathcal{Q}[\Omega(t')]$ is an integration measure over the space of functions $\Omega(t')$, $\overline{\int \int}$ stands for the operation of path integration, and $\mathcal{F}(t')$ is a suitable test function.

The reference lifetime distribution is introduced as the solution of the differential equation:

$$d\xi_i^{*(\text{ref})}(\tau; t_0 + \tau)/d\tau = -\Omega(t_0 + \tau) \xi_i^{*(\text{ref})}(\tau; t_0 + \tau) \quad (85)$$

which is

$$\xi_i^{*(\text{ref})}(\tau; t) = \Omega(t - \tau) \exp[-\int_{t-\tau}^t \Omega(t') dt'] \quad (86)$$

where the integration constant has been determined from the normalization condition of the lifetime distribution, $\int_0^\infty \xi_i^{*(\text{ref})}(\tau; t) d\tau = 1$. The normal lifetime distribution, $\xi_i^*(\tau; t)$ may be represented by a superposition of reference functions:

$$\xi_i^*(\tau; t) = \overline{\int \int \xi_i^{*(\text{ref})}(\tau; t) \mathcal{P}[\Omega(t')] \mathcal{Q}[\Omega(t')] = \overline{\int \int \Omega(t - \tau) \exp[-\int_{t-\tau}^t \Omega(t') dt'] \mathcal{P}[\Omega(t')] \mathcal{Q}[\Omega(t')] \quad (87)$$

By comparing eq 87 with the analytic expression (eq 16) for the normal lifetime distribution $\xi_i^*(\tau; t)$, we notice that the probability density functional $\mathcal{P}[\Omega(t')] \mathcal{Q}[\Omega(t')]$ is given by a functional Dirac δ distribution:

$$\mathcal{P}[\Omega(t')] \mathcal{Q}[\Omega(t')] = \Delta[\Omega(t') - \lambda_i^+(t')] \mathcal{Q}[\Omega(t')] \quad (88)$$

It follows that the characteristic frequency can have only one value different from zero, which is equal to the infinitesimal rate $\lambda_i^+(t)$ of generation of a new intermediate at time t defined by eq 12.

We notice that the δ distribution 88 is not negative and that it is properly normalized to unity. The choice (eq 86) for the reference time distribution has solved the problem of negative probabilities. This alternative approach is very different from the spectral kinetic analysis presented in the literature. The purpose of traditional kinetic spectral analysis is to decompose an observed or calculated time distribution into contributions of different modes, each mode having an exponential distribution. Our first method, suggested in the preceding section is in the spirit of this traditional approach. The approach suggested in this section is based on the reference distribution 86, which is an exponential in the lifetime τ only in the trivial case where the characteristic frequency is time independent, a situation which correspond to a steady state, not to a limit cycle.

The approach developed in this section is useful for computing the influence of environmental fluctuations on the lifetime distributions, based on the method characteristic functionals.²⁰ Let us assume that the system under study is perturbed by the random fluctuations of a number of environmental parameters

$$\mathbf{z}(t) = [z_1(t), z_2(t), \dots] \quad (89)$$

we assume that the random fluctuations of the environmental parameters are stationary and that for any realization of the vector $\mathbf{z}(t)$ the solutions of the kinetic equations tend toward time-dependent normal regimes, which up to a constant phase factor, are independent of the initial state of the system; these normal regimes may correspond to many limit cycles which, in general, are different from the purely deterministic limit cycle corresponding to $\mathbf{z}(t) = 0$. We are interested in the average behavior of the normal lifetime distribution $\xi_i^*(\tau; t)$ over all possible realizations of the random vector $\mathbf{z}(t)$:

$$\xi_i^*(\tau; t) = \langle \xi_i^*[(\tau; t); \mathbf{z}(t')] \rangle \quad (90)$$

For computing the average eq 90 we express the effective rate $\lambda_i^+(t)$ as a functional of $\mathbf{z}(t)$ and insert eq 16 into eq 90, resulting in

$$\xi_i^*(\tau; t) = \langle \lambda_i^+[(t - \tau); \mathbf{z}(t')] \exp[-\int_{t-\tau}^t \lambda_i^+[(t''); \mathbf{z}(t'')] dt''] \rangle \quad (91)$$

Now we integrate eq 91 over the lifetime τ from $\tau = \tau$ to $\tau = \infty$ and assume that the integral over τ and the average over the environmental variables commute. The integral in the right hand side of the resulting equation can be evaluated analytically. By differentiating the result of the integration term by term with respect to τ we come to

$$\xi_i^*(\tau; t) = -\frac{\partial}{\partial \tau} \langle \exp[\int_{t-\tau}^t \lambda_i^+[(t''); \mathbf{z}(t'')] dt''] \rangle \quad (92)$$

Now we identify the effective rate $\lambda_i^+[(t''); \mathbf{z}(t'')]$ with the characteristic frequency $\Omega(t'')$:

$$\Omega(t'') = \lambda_i^+[(t''); \mathbf{z}(t'')] \quad (93)$$

In particular, the effective rate $\lambda_i^+(t)$, characteristic for a system without environmental fluctuations ($\mathbf{z}(t) = 0$), is equal to the average value of the characteristic frequency:

$$\lambda_i^+(t) = \langle \Omega(t') \rangle \quad (94)$$

By using eqs 84 and 93, eq 92 can be rewritten as

$$\begin{aligned} \xi_i^*(\tau; t) &= -\frac{\partial}{\partial \tau} \langle \exp[-\int_{t-\tau}^t \Omega(t') dt'] \rangle = \\ &= -\frac{\partial}{\partial \tau} \overline{\int \int \exp[-\int_{t-\tau}^t \Omega(t') dt'] \mathcal{P}[\Omega(t')] \mathcal{Q}[\Omega(t')] =} \\ &= -\frac{\partial}{\partial \tau} \mathcal{K}[\mathcal{F}(t) = j(h(t - \tau) - h(t))] \quad (95) \end{aligned}$$

If the stochastic properties of the environmental variables $\mathbf{z}(t) = [z_1(t), z_2(t), \dots]$ and the functional dependence of the effective rate $\lambda_i^+[(t''); \mathbf{z}(t'')]$ on $\mathbf{z}(t')$ are known, then the stochastic properties of the characteristic frequency $\Omega(t')$ can be easily evaluated. In this article we express these stochastic properties in terms of the cumulants $\langle\langle \Omega(t'_1) \Omega(t'_2) \dots \Omega(t'_m) \rangle\rangle$ which are assumed to be finite. It is well-known from quantum field theory, as well as from mathematical statistics²¹ that the logarithm of the characteristic functional $\mathcal{K}[\mathcal{F}(t')]$ can be expressed as a multivariate functional Taylor series expansion in terms of the different powers of the components of the test function $\mathcal{F}(t')$; in this series the coefficients of the expansion are given by the cumulants of the fluctuating environmental variables:

$$\ln \mathcal{K}[F(t')] = \sum_{m=1}^{\infty} \frac{(-j)^m}{m!} \int \dots \int F(t'_1) \dots F(t'_m) \langle \langle \Omega(t'_1) \dots \Omega(t'_m) \rangle \rangle dt'_1 \dots dt'_m \quad (96)$$

By combining eqs 95 and 96, we obtain a cumulant expansion for the average lifetime distribution:

$$\begin{aligned} \xi_i^*(\tau; t) &= -\frac{\partial}{\partial \tau} \exp \left\{ \sum_{m=1}^{\infty} \frac{(-1)^m}{m!} \int_{t-\tau}^t \dots \int_{t-\tau}^t \langle \langle \Omega(t'_1) \dots \Omega(t'_m) \rangle \rangle dt'_1 \dots dt'_m \right\} \\ &= -\frac{\partial}{\partial \tau} \{ \Phi_i^*(\tau; t) T_i^*(\tau; t) \} = \xi_i^*(\tau, t) T_i^*(\tau; t) - \Phi_i^*(\tau; t) \frac{\partial}{\partial \tau} T_i^*(\tau; t) \quad (97) \end{aligned}$$

where $\xi_i^*(\tau; t)$ and $\Phi_i^*(\tau; t)$ are the lifetime distribution and the survival function of a molecule in absence of environmental fluctuations, and the amplification factor

$$\mathcal{T}_i^*(\tau; t) = \exp \left\{ \sum_{m=2}^{\infty} \frac{(-1)^m}{m!} \int_{t-\tau}^t \dots \int_{t-\tau}^t \langle \langle \Omega(t'_1) \dots \Omega(t'_m) \rangle \rangle dt'_1 \dots dt'_m \right\} \quad (98)$$

expresses the contribution of environmental fluctuations. By introducing the survival function for a system with environmental fluctuations,

$$\tilde{\Phi}_i^*(\tau; t) = \langle \Phi_i^*(\tau; t; \mathbf{z}(t')) \rangle = \int_{\tau}^{\infty} \xi_i^*(\tau'; t) d\tau' \quad (99)$$

Equation 97 turns into a simpler form,

$$\tilde{\Phi}_i^*(\tau; t) = \Phi_i^*(\tau; t) \mathcal{T}_i^*(\tau, t) \quad (100)$$

The ratio of the average lifetimes $\langle \tau(\tilde{t}) \rangle_i^*$ and $\langle \tau(t) \rangle_i^*$ of a molecule, in the presence or absence of environmental fluctuations, can be expressed as an average of the amplification factor $\mathcal{T}_i^*(\tau; t)$. We express the average lifetimes for a system with and without environmental fluctuations, in terms of the survival functions $\tilde{\Phi}_i^*(\tau; t)$ and $\Phi_i^*(\tau; t)$:

$$\begin{aligned} \langle \tau(t) \rangle_i^* &= \int_0^{\infty} \tau \xi_i^*(\tau; t) d\tau = \int_0^{\infty} \Phi_i^*(\tau; t) d\tau, \quad \langle \tau(\tilde{t}) \rangle_i^* = \\ &= \int_0^{\infty} \tau \xi_i^*(\tau; t) d\tau = \int_0^{\infty} \tilde{\Phi}_i^*(\tau; t) d\tau \quad (101) \end{aligned}$$

From eqs 100 and 101 we come to

$$\frac{\langle \tau(\tilde{t}) \rangle_i^*}{\langle \tau(t) \rangle_i^*} = \int_0^{\infty} \mathcal{T}_i^*(\tau, t) \Phi_i^*(\tau; t) d\tau / \int_0^{\infty} \Phi_i^*(\tau; t) d\tau \quad (102)$$

For a more detailed analysis we need to know the stochastic properties of the environmental variables $\mathbf{z}(t) = [z_1(t), z_2(t), \dots]$ or of the characteristic frequency $\Omega(t)$. For illustration, we discuss the simple case of stationary Gaussian fluctuations for which the computations can be carried out analytically. According to eq 94, the average value of the characteristic frequency $\Omega(t)$ is equal to the effective rate $\lambda_i^+(t)$ in the absence of environmental fluctuations. The average characteristic frequency $\langle \Omega(t) \rangle$ is obviously time-dependent. We assume

that the fluctuations around this nonstationary average value

$$\Delta\Omega(t) = \Omega(t) - \langle \Omega(t) \rangle \quad (103)$$

are random variables obeying stationary Gaussian statistics. For a Gaussian process all cumulants of order bigger than two are equal to zero. It follows that we can describe the stochastic properties of the characteristic frequency by the first two cumulants:

$$\langle \langle \Omega(t) \rangle \rangle = \langle \Omega(t) \rangle = \lambda_i^+(t) \quad (104)$$

$$\langle \langle \Omega(t_1) \Omega(t_2) \rangle \rangle = \langle \Delta\Omega(t_1) \Delta\Omega(t_2) \rangle = \mathcal{C}(|t_1 - t_2|) \quad (105)$$

where, due to the stationarity of the stochastic process considered, the autocorrelation function $\langle \Delta\Omega(t_1) \Delta\Omega(t_2) \rangle = \mathcal{C}(|t_1 - t_2|)$ of the characteristic frequency depends only on the absolute value of the time difference, $t_1 - t_2$. This type of Gaussian model is very popular in the literature of dynamical disorder; it has been introduced almost 50 years ago for describing the line shapes in experiments of magnetic resonance²² and is has been further applied for describing a broad class of environmental fluctuations in physics, chemistry, and biology.²³

For a Gaussian process characterized by eqs 104–105, the amplification factor $\mathcal{T}_i^*(\tau; t)$ can be easily evaluated from eq 98:

$$\mathcal{T}_i^*(\tau; t) = \exp \left\{ \frac{1}{2} \int_{t-\tau}^t \int_{t-\tau}^t \mathcal{C}(|t_1 - t_2|) dt_1 dt_2 \right\} = \exp \{ \mathcal{J}(\tau) \}, \quad \text{independent of } t \quad (106)$$

where

$$\mathcal{J}(\tau) = \int_0^{\infty} (\tau - \theta) \mathcal{C}(\theta) d\theta \quad (107)$$

Usually in the literature the correlation function is represented as a sum of contributions of different normal modes²⁴

$$\begin{aligned} \langle \Delta\Omega(t_1) \Delta\Omega(t_2) \rangle &= \mathcal{C}(|t_1 - t_2|) = \sum_q c_q \exp[-v_q |t_1 - t_2|] + \\ &+ \int_q c(q) \exp[-v(q) |t_1 - t_2|] dq \quad (108) \end{aligned}$$

where c_q , $c(q)$, v_q and $v(q)$ are amplitude and frequency factors attached to the different normal modes. In general, both c_q and v_q are complex and their values must be chosen in such a way that the corresponding Gaussian process is physically consistent. If the mode spectrum is purely discrete then in eq 108 the integral term is missing and the stochastic process, although generally non-Markovian, has short memory. The Markovian case corresponds to a single exponential, that is, to a single mode. For a discrete spectrum the Markovian approximation is accurate for large time differences because in this case the main contribution to the sum in eq 108 is given by a single exponential which corresponds to the frequency with the smallest absolute value. A very interesting situation is the one for which the mode spectrum has a continuum branch. In this case, the tail of the correlation function may obey a scaling law of the inverse power type and the system may display long memory.

We start out by investigating the case of discrete spectrum. We require that the value of the factors b_q and v_q must be consistent with the following physical constraints: 1. For a time difference equal to zero the autocorrelation function is equal to the dispersion of the characteristic frequency at time t , $\langle [\Delta\Omega(t)]^2 \rangle$, which, by definition, must be nonnegative. 2. Since the characteristic frequency is a real function of time, the modes with complex frequencies v_q must occur in conjugated pairs. 3.

For large times the autocorrelation function of the characteristic frequency must decay to zero.

We keep in eq 108 only the contribution of discrete spectrum and write separately the contribution of real eigenvalues $\nu_q^{(\text{real})} = \text{real}$ and of complex eigenvalues $\nu_q^{(\text{compl})} = m_q \pm j\sigma_q$. After some calculations we obtain

$$\begin{aligned} \mathcal{C}(|t_1 - t_2|) = & \sum_{\text{real values}} c_q^{(\text{real})} \exp[-\nu_q^{(\text{real})}|t_1 - t_2|] + \\ & \sum_{\text{complex values}} c_q^{(\text{compl})} \exp[-\nu_q^{(\text{compl})}|t_1 - t_2|] = \\ & \sum_{\text{real values}} c_q^{(\text{real})} \exp[-\nu_q^{(\text{real})}|t_1 - t_2|] + \sum_{\text{complex values}} 2\{a_q \cos \\ & [\sigma_q|t_1 - t_2|] + b_q \sin[\sigma_q|t_1 - t_2|]\} \exp[-\mu_q|t_1 - t_2|] \quad (109) \end{aligned}$$

where a_q and b_q are the real and imaginary parts of the complex amplitude factors, $c_q^{(\text{compl})} = a_q \pm jb_q$. In order that the constraints 1–4 be valid we introduce the following restrictions for the parameters in eq 110

$$c_q^{(\text{real})}, \quad a_q \geq 0, \quad b_q = 0 \quad (110)$$

$$\nu_q^{(\text{real})}, \quad \mu_q \geq 0 \quad (111)$$

The restrictions 111 ensure that the dispersion of the characteristic frequency is non-negative whereas the restrictions 112 are necessary in order that the autocorrelation function tends to zero for large time differences. By inserting eqs 107 and 110 into eq 106 after lengthy calculation we obtain the following expression for the amplification factor

$$\mathcal{T}_i^*(\tau; t) = \exp\{\Theta_i^*(\tau)\} \quad (112)$$

where the phase factor $\Theta_i^*(\tau)$ is given by

$$\begin{aligned} \Theta_i^*(\tau) = & \tau \left[\sum_{\text{real values}} \frac{c_q^{(\text{real})}}{\nu_q} + \sum_{\text{complex values}} \frac{2(a_q \mu_q + b_q \sigma_q)}{(\mu_q)^2 + (\sigma_q)^2} \right] - \\ & \sum_{\text{real values}} \frac{c_q^{(\text{real})}}{(\nu_q)^2} + 2 \sum_{\text{complex values}} \frac{c_q^{(\text{real})}}{(\nu_q)^2} + \\ & \left[\frac{a_q[(\sigma_q)^2 - (\mu_q)^2] - 2b_q \mu_q \sigma_q}{[(\mu_q)^2 + (\sigma_q)^2]^2} \right] + \sum_{\text{real values}} \frac{c_q^{(\text{real})}}{(\nu_q)^2} \exp(-\nu_q \tau) + \\ & \frac{2}{[(\mu_q)^2 + (\sigma_q)^2]^2} \sum_{\text{complex values}} \{a_q[(\mu_q)^2 - (\sigma_q)^2] \cos(\sigma_q \tau) + \\ & 2b_q \mu_q \sigma_q \} \exp(-\mu_q \tau) + \frac{2}{[(\mu_q)^2 + (\sigma_q)^2]^2} \sum_{\text{complex values}} \times \\ & \{b_q[(\mu_q)^2 - (\sigma_q)^2] \sin(\sigma_q \tau) - 2a_q \mu_q \sigma_q \} \exp(-\mu_q \tau) \quad (113) \end{aligned}$$

According to eqs 111–114 for large lifetimes the amplification factor $\mathcal{T}_i^*(\tau; t)$ diverges exponentially to infinity:

$$\mathcal{T}_i^*(\tau; t) \sim \begin{cases} \exp\{\mathcal{J}_i^* \tau^2\} & \text{as } \tau \rightarrow 0 \\ \exp\{\mathcal{J}_i^* \tau\} & \text{as } \tau \rightarrow \infty \end{cases} \quad (114)$$

where the effective rates of increase \mathcal{J}_i^* and \mathcal{J}_i^* are given by

$$\mathcal{J}_i^* = \frac{1}{2} \sum_{\text{real values}} c_q^{(\text{real})} + \sum_{\text{complex values}} a_q > 0 \quad (115)$$

$$\mathcal{J}_i^* = \sum_{\text{real values}} \frac{c_q^{(\text{real})}}{\nu_q} + \sum_{\text{complex values}} \frac{2(a_q \mu_q + b_q \sigma_q)}{(\mu_q)^2 + (\sigma_q)^2} > 0 \quad (116)$$

We expand the generation rate $\lambda_i^+(t)$ in a Fourier series and separate the temporal average value $\bar{\lambda}_i^+$ given by eq 36:

$$\lambda_i^+(t) = \bar{\lambda}_i^+ + \Delta\lambda_i^+(t) \quad (117)$$

where $\Delta\lambda_i^+(t)$ is the periodic component of $\lambda_i^+(t)$ with average value zero given by the sum of the Fourier components of order different from zero; $\Delta\lambda_i^+(t)$ can be expressed as a real Fourier series

$$\Delta\lambda_i^+(t) = \sum_{m=1}^{\infty} A_i^{(s)(m)} \sin\left[\frac{2\pi m t}{T} + \vartheta_i^{(m)}\right] \quad (118)$$

By using eqs 118–119 we can express the survival function $\Phi_i^*(\tau; t)$ as

$$\Phi_i^*(\tau; t) = \exp(-\tau \bar{\lambda}_i^+) \Psi_i^*(\tau; t) \quad (119)$$

where $\Psi_i^*(\tau; t)$ is a periodic function of the lifetime τ

$$\begin{aligned} \Psi_i^*(\tau; t) = \\ \exp\left\{ \sum_{m=1}^{\infty} A_i^{(s)(m)} \frac{T}{\pi m} \cos\left(\frac{\pi m \tau}{T}\right) \cos\left(\frac{\pi m (2t - \tau)}{T} + \vartheta_i^{(m)}\right) \right\} \quad (120) \end{aligned}$$

Now we evaluate the ratio of the average lifetimes by using eq 102:

$$\begin{aligned} \frac{\langle \tau(t) \rangle_i^*}{\langle \tau(t) \rangle_i^*} = \int_0^{\infty} \mathcal{T}_i^*(\tau; t) \exp(-\tau \bar{\lambda}_i^+) \Psi_i^*(\tau; t) d\tau / \\ \int_0^{\infty} \exp(-\tau \bar{\lambda}_i^+) \Psi_i^*(\tau; t) d\tau \quad (121) \end{aligned}$$

For small fluctuations the amplification factor $\mathcal{T}_i^*(\tau; t)$ is very close to unity and the two average lifetimes are practically equal. As the intensity of fluctuations increases the effective \mathcal{J}_i^* rate also increases and the average lifetime in the presence of environmental fluctuations increases. In the limit $\mathcal{J}_i^* \rightarrow \bar{\lambda}_i^+$ the average lifetime diverges to infinity:

$$\langle \tau(t) \rangle_i^* \rightarrow \infty \text{ as } \mathcal{J}_i^* \rightarrow \bar{\lambda}_i^+ \quad (122)$$

The above analysis shows that the environmental fluctuations lead to an increase of the average lifetime of the active intermediates in the system.

In the case of continuum spectrum we limit our analysis to the case of real frequency factors distributed according to a self-similar power law. In eq 108 we keep only the continuum component of the spectrum and identify the frequency factor ν with the integration variable q . We obtain:

$$\langle \Delta\Omega(t_1) \Delta\Omega(t_2) \rangle = \mathcal{C}(|t_1 - t_2|) = \int_{\nu} c(\nu) \exp[-\nu|t_1 - t_2|] d\nu \quad (123)$$

We assume the frequency spectrum displays an ultraviolet cutoff for a maximum frequency $\nu = \nu_M$ and that for $\nu_M \geq \nu \geq 0$ the frequency factors are distributed according to the power law:²⁵

$$c(v)dv \sim \mathcal{M}dv^H = \mathcal{M}Hv^{H-1}dv \quad (124)$$

The amplification factor $\mathcal{T}_i^*(\tau; t)$ can be easily evaluated from eq 106 and eqs 123 and 124:

$$\begin{aligned} \mathcal{T}_i^*(\tau; t) = & \exp \left\{ \frac{1}{2} \int_{t-\tau}^t \int_{t-\tau}^t \int_0^{v_M} \exp[-v|t_1 - t_2|] \mathcal{M}Hv^{H-1} dv dt_1 dt_2 \right\} = \\ & \exp(\mathcal{J}(\tau)) \sim \begin{cases} \exp(\mathcal{S}_i^* \tau^2) & \text{as } \tau \rightarrow 0 \\ \exp(\mathcal{B}_i^* \tau^{2-H}) & \text{as } \tau \rightarrow \infty \end{cases} \quad (125) \end{aligned}$$

where the phase factor $\mathcal{J}(\tau)$ and the effective rates of increase \mathcal{S}_i^* and \mathcal{B}_i^* are given by

$$\begin{aligned} \mathcal{J}(\tau) = & \frac{\mathcal{M}}{(v_M)^{2-H}} [\exp(-v_M \tau) + v_M \tau - 1] + \\ & \frac{\mathcal{M}(v_M)^{H-2}}{(1-H)(2-H)} \times \{ (v_M \tau)^{2-H} \gamma(H+1, v_M \tau) + 2 - \\ & 2H + v_M \tau(2-H) + [(v_M \tau)^2 + v_M \tau H + H-2] \exp(-v_M \tau) \} \quad (126) \end{aligned}$$

$$\mathcal{S}_i^* = \frac{1}{2} \mathcal{M}(v_M)^H \quad (127)$$

$$\mathcal{B}_i^* = \frac{\mathcal{M}\Gamma(1+H)}{(1-H)(2-H)} \quad (128)$$

and

$$\begin{aligned} \gamma(a, x) = & \int_0^x y^{a-1} \exp(-y) dy, \quad a > 0, \quad x \geq 0 \quad \text{and} \\ \Gamma(a) = & \int_0^\infty y^{a-1} \exp(-y) dy, \quad a > 0 \quad (129) \end{aligned}$$

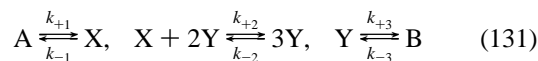
are the incomplete and complete gamma functions of the first kind, respectively. In this case, as the lifetime of a molecule τ increases the amplification factor $\mathcal{T}_i^*(\tau; t)$ increases faster than in the case of short memory. It is easy to check from eqs 122 and 125 that for long memory the average lifetime of an intermediate is infinite

$$\langle \tau(t) \rangle_i^* = \infty \quad (130)$$

The general conclusion of this section is that there is a direct relationship between the strength and memory of environmental fluctuations and the lifetimes of active intermediates: the average lifetimes increase with the increase of environmental fluctuations. For short memory there is a threshold value of the environmental fluctuations for which the average lifetimes diverge to infinity. In the case of long memory the average lifetimes are infinite for any intensity of environmental fluctuations. The occurrence of infinite average lifetimes for fluctuations with long memory is an expected result: the infinite moments are a typical feature of fractal random processes.²⁶⁻²⁷

8. Example

For illustrating the asymptotic behavior of the lifetime distributions of active intermediates for a stable limit cycle we have performed a numerical study of lifetime distributions in a system of the Selkov type.²⁸ The Selkov model is given by the reaction scheme:



where A and B are stable species with concentrations kept constant by interaction with large external reservoirs and X and Y are reaction intermediates with concentrations variable in time. The reaction mechanism 131 may display a stable limit cycle for certain values of the rate coefficients and of the concentrations of stable species A and B. The kinetic equations of the Selkov model 131 are integrated numerically. For large times the process is approaching a stable limit cycle and the time variation of X and Y becomes periodic. The theory developed in this article may be used for evaluating the time dependence and the lifetime dependence of the lifetime distributions of the reaction intermediates X and Y. Figures 1 and 2 display such a dependence for the species X for two different initial conditions. As expected, for small times, the lifetime distributions are narrow and become broad for large times. After about 20 time units, the lifetime distributions display a self-repeating, periodic pattern in time which seems to be the same in both cases. Figure 3 displays the difference $\Delta \xi(\tau; t) = \xi_\alpha(\tau; t) - \xi_\beta(\tau; t)$ between the distribution functions shown in Figures 1 and 2 as a function of time t and of the lifetime τ . Figure 3 shows clearly that, even though for large times the functions $\xi_{\alpha, \beta}(\tau; t)$ have the same shape, they have different phases. It is easy to check that for $t > 20$ the phase difference between the lifetime distributions $\xi_\alpha(\tau; t)$ and $\xi_\beta(\tau; t)$ is about $\Delta \varphi \cong 0.48\pi$, and that, up to this phase difference they are identical

$$\begin{aligned} \xi_\alpha(\tau; t) \cong & \xi_\beta(\tau; t - \Delta \varphi) \text{ for } t > 20, \quad \text{where} \\ & \Delta \varphi \cong 0.48\pi \quad (132) \end{aligned}$$

Figure 4 displays the phase-corrected difference

$$\begin{aligned} \Delta \xi_{\text{phase}}(\tau; t) = & \xi_\alpha(\tau; t) - \xi_\beta(\tau; t - \Delta \varphi) \quad \text{with} \\ & \Delta \varphi \cong 0.48\pi \quad (133) \end{aligned}$$

of the lifetime distributions $\xi_\alpha(\tau; t)$ and $\xi_\beta(\tau; t)$ as a function of the time t and the lifetime τ . For large times the phase-corrected difference $\Delta \xi_{\text{phase}}(\tau; t)$ tends toward zero, which confirms the validity of the H -theorem proven in the article.

For performing a spectral kinetic analysis it is necessary that the lifetime distribution is known for a broad range of values of the lifetime. Unfortunately our numerical computations are not sufficiently accurate for a detailed spectral kinetic analysis. We have evaluated the time and frequency dependence of the real and imaginary parts, $\chi'_i(\omega; t)$ and $\chi''_i(\omega; t)$, of the complex susceptibility function $\Xi_i^*(\omega; t)$, shown in Figures 5 and 6. We notice that for large times these two functions have a shape close to a Lorentzian profile, which suggests that in the long run the lifetime distributions have a shape close to an exponential. This assumption is consistent with the data presented in Figure 7, which displays the asymptotic behavior of the average lifetime $\langle \tau(t) \rangle$ of the intermediate X and of the variation $\epsilon(t)$ of the absolute value of the dispersion of the lifetime $\tau(t)$. The small value of $\epsilon(t)$ also suggests that the shape of the lifetime distribution is close to an exponential.

9. Discussion

The analysis of the circumstances under which a complex process forgets its past is an important topic of nonlinear dynamics. In the case of nonlinear kinetics this type of analysis is usually limited to a purely deterministic study of the asymptotic behavior of the solutions of kinetic equations. In this article we have dealt with the more complicated case when

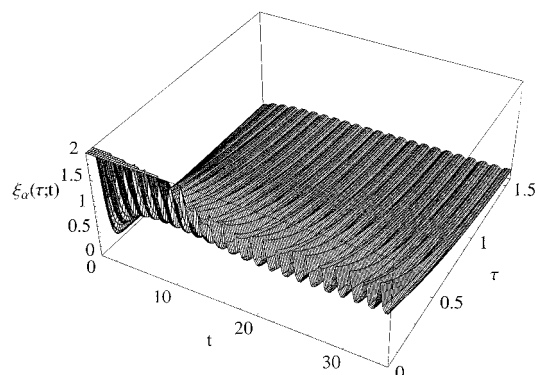


Figure 1. The time and lifetime dependence of the lifetime distributions $\xi_{\alpha,\beta}(\tau;t)$ of the active intermediate X for the Selkov model (131) corresponding to two different initial conditions. In both cases for small times the lifetime distributions are very narrow, close to a delta function shape and tend to become broad for large times. After about 20 time units the lifetime distributions corresponding to the two initial conditions become periodic in time with a period of about 0.98π time units and have the same shape; for large times the phase difference between the two solutions is $\Delta\varphi \cong 0.48\pi$ time units.

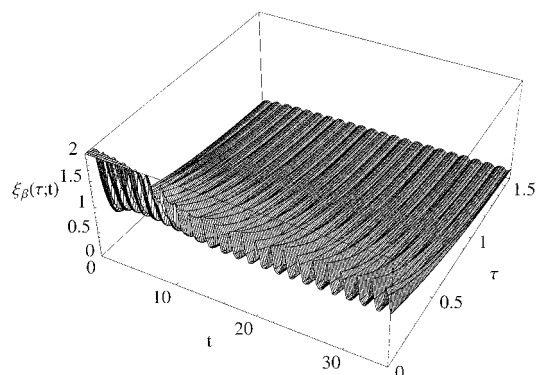


Figure 2. The time and lifetime dependence of the lifetime distributions $\xi_{\alpha,\beta}(\tau;t)$ of the active intermediate X for the Selkov model (131) corresponding to two different initial conditions. In both cases for small times the lifetime distributions are very narrow, close to a delta function shape and tend to become broad for large times. After about 20 time units the lifetime distributions corresponding to the two initial conditions become periodic in time with a period of about 0.98π time units and have the same shape; for large times the phase difference between the two solutions is $\Delta\varphi \cong 0.48\pi$ time units.

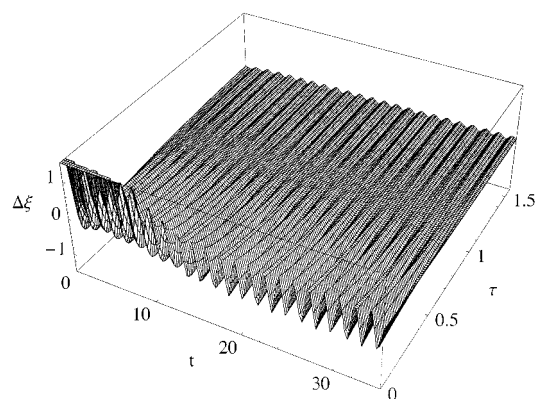


Figure 3. The time and lifetime dependence of the difference $\Delta\xi(\tau;t) = \xi_{\alpha}(\tau;t) - \xi_{\beta}(\tau;t)$ of the lifetime distributions $\xi_{\alpha,\beta}(\tau;t)$ of the active intermediate X represented in Figures 1 and 2. For large time this difference tends toward a periodic function of time.

the description of the process is semistochastic and given in terms of the lifetime distributions of the different chemicals presents in the system, rather than in terms of concentrations.

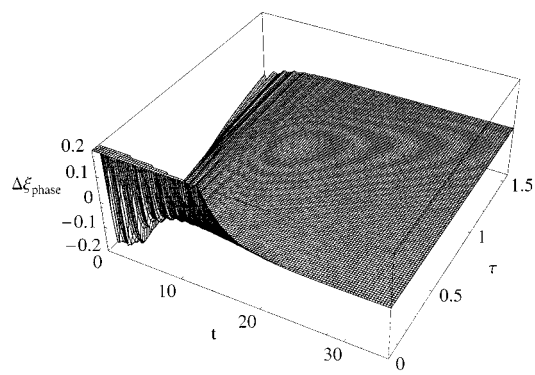


Figure 4. The time and lifetime dependence of the phase-corrected difference phase $\Delta\xi_{\text{phase}}(\tau;t) = \xi_{\alpha}(\tau;t) - \xi_{\beta}(\tau;t - \Delta\varphi)$ of the lifetime distributions $\xi_{\alpha,\beta}(\tau;t)$ of the active intermediate X represented in Figures 1 and 2, with $\Delta\varphi \cong 0.48\pi$. For large time the phase-corrected difference tends toward zero, confirming the validity of the H -theorem for the lifetime distributions.

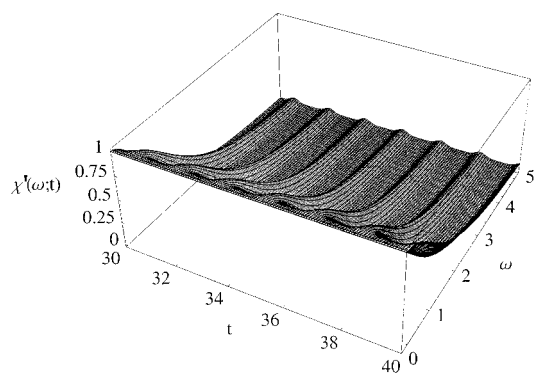


Figure 5. The time- and frequency-dependence of the real and imaginary parts $\chi'_{i}(\omega;t)$ and $\chi''_{i}(\omega;t)$ of the complex susceptibility function $\Xi_i^*(\omega;t)$. After a long time, both $\chi'_{i}(\omega;t)$ and $\chi''_{i}(\omega;t)$ are periodic in time. For constant time the frequency dependence of the real and imaginary parts of the complex susceptibility function are close to a Lorentzian shape.

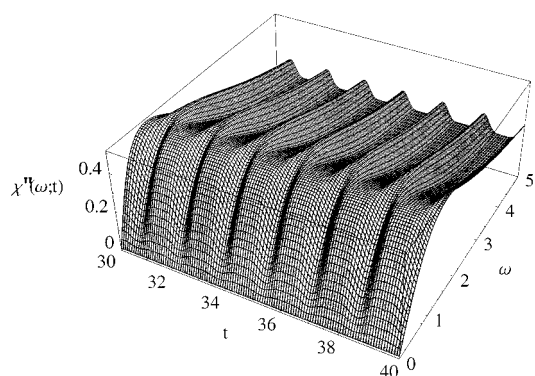


Figure 6. The time- and frequency-dependence of the real and imaginary parts $\chi'_{i}(\omega;t)$ and $\chi''_{i}(\omega;t)$ of the complex susceptibility function $\Xi_i^*(\omega;t)$. After a long time, both $\chi'_{i}(\omega;t)$ and $\chi''_{i}(\omega;t)$ are periodic in time. For constant time the frequency dependence of the real and imaginary parts of the complex susceptibility function are close to a Lorentzian shape.

We have assumed that the size of the system is large enough that the intrinsic concentration fluctuations can be neglected and the kinetics of the process can be described in terms of the deterministic mass-action law. For such a system, even though the concentrations are not random, the lifetimes of the different chemicals in the system are random variables and their stochastic properties can be computed by using a system of balance equations for the lifetime distributions.

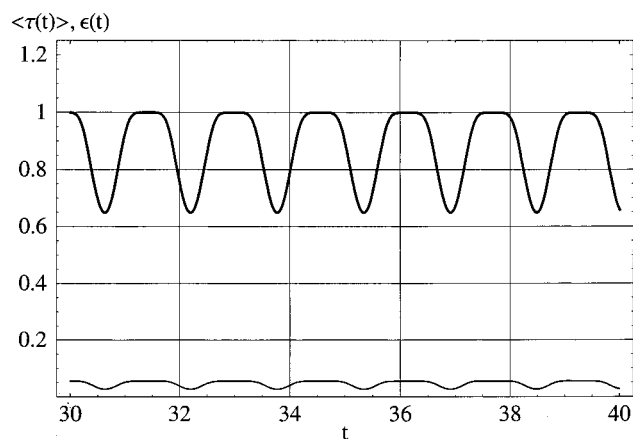


Figure 7. The asymptotic behavior of the average lifetime $\langle \tau(t) \rangle$ of the intermediate X and of the variation $\epsilon(t)$ of the absolute value of the dispersion of the lifetime, equation 67. Both functions vary periodically in time. The small absolute value of $\epsilon(t)$ suggests that for a given time the lifetime distribution has a shape close to an exponential.

We have limited our analysis to the simplest type of nonlinear chemical systems with nontrivial dynamics, characterized by a stable limit cycle for the concentrations of the active intermediates. For a stable limit cycle a chemical system partially forgets its past: usually, although the shape of the attractor, the stable limit cycle, is independent of the initial conditions, the phases of the different chemicals at the limit cycle depend on the initial conditions. By using an H -(Lyapunov) function we have shown that a similar property exists for the lifetime distributions of the different chemicals: In the long run, up to constant phase factors they tend toward normal forms, which are periodic functions of time and independent of the initial conditions.

We have also investigated the possibilities of determining the normal forms of the lifetime distributions by means of tracer experiments. For circumventing the difficulties due to the fact that the lifetime distributions depend both on time and on lifetime, we have suggested a frequency response tracer experiment. Such an experiment allows the direct measurement of the frequency and time dependence of the Fourier transforms of the lifetime distributions. These Fourier transforms are both the characteristic functions of the lifetime distributions and generalized susceptibilities characterizing the response of the system to an external excitation. We have investigated the analytic properties of the complex susceptibility functions and shown that their real and imaginary parts are related by means of a set of integral equations due to causality. These integral equations are generalizations of the Kramers–Kronig relationships for systems with complex susceptibilities depending both on frequency and time.

The kinetic spectrum analysis is a powerful tool used in the literature for the analysis of the kinetic behavior of complex chemical processes.^{15–17} In this article we have extended the kinetic spectrum analysis to the study of lifetime distributions and investigated the possibilities of extracting various parameters from the data provided by tracer experiments, such as the distributions of the characteristic frequencies and of the lifetimes and their moments and cumulants. This study is the first step in developing an experimental technique of studying the reaction mechanisms by using the lifetime distributions and tracer experiments, rather than recording the time-dependence of the chemicals.

By starting out from an alternative approach for the kinetic spectrum analysis, we have suggested a general approach for evaluating the influence of environmental fluctuations on the

lifetime distributions. We have assumed that the intrinsic concentration fluctuations are much smaller than the environmental fluctuations and can be neglected. On the basis of this hypothesis, we have developed an exact method of computing the dynamical averages of the lifetime distributions in terms of the amplification factor due to external fluctuations, which can be expressed as a functional of the cumulants of the characteristic frequency of the process. The general approach developed has been applied to the particular case of Gaussian fluctuations with short and long memory. The correlation function of the characteristic frequency has been represented as a superposition of exponentials attached to different modes and the amplification factor has been evaluated exactly. The passage from short memory to long memory corresponds to a transition from finite average lifetimes to infinite average lifetimes. The occurrence of infinite average lifetimes is hardly a surprise, since the occurrence of infinite moments is a common feature of statistical fractal distributions.^{26–27} According to the literature of fractal statistics, the standard interpretation of infinite moments is related to the lack of the existence of a characteristic scale of the random variable. For such systems the average values are meaningless; only the probability distributions itself, and other functions depending on it, such as the amplification factor, are physically significant. The experiments dealing with these systems usually lead to finite averages, because of the finite range of variation of the random variables accessible to measurement. An increase without limits of the average values with the increase of the range of measurements is consistent with the theoretical average values equal to infinity.

We intend to develop the approach presented in this paper in the following directions. An interesting idea is to use the lifetime distributions obtained from frequency response tracer experiments for identifying the reaction mechanisms in complex chemical systems far from equilibrium. A first step in achieving this goal is the generalization of the present theory of the lifetime to the more complex notion of transit time. For many complex chemical processes it is possible to identify one or more molecular fragments which remain unchanged during a complicated succession of chemical reactions. For such a molecular fragment it is possible to introduce a notion similar to the lifetime of a molecule, the “transit time” which is the time interval that elapses from the entrance of the fragment in the system until its exit from the system.²⁹ In the particular case of a single reaction step, the transit time is identical with the lifetime studied in this article. In a recent paper³⁰ we have already studied the main properties of the transit time for some types of biochemical reactions. It is necessary to extend the analysis presented in the present article for the lifetime of a molecule to the transit time of a molecular fragment. An important step is to suggest a frequency response tracer experiment for evaluating the transit time distributions.

Another important problem, already mentioned in section 7 is to investigate the relationships between the semistochastic approach developed in this article and the purely stochastic approaches to chemical kinetics based on the use of the master equation. The theoretical method of investigating this problem is based on the use of Poissonian representation techniques.^{18–19}

A third direction of research is related to the problem of environmental fluctuations. The environmental fluctuations enter multiplicatively the evolution equations, a feature which is typical for systems with dynamical disorder.³¹ Recent studies of dynamical disorder have shown that for such processes there is a coupling between the intrinsic and external fluctuations, resulting in an intermittent behavior and other exotic coupling

effects.³² In the present paper we have neglected the intrinsic fluctuations. Future research should include both the internal fluctuations, described for example by the chemical master equation and the external fluctuations, described by the characteristic functional of the characteristic frequency. Work on this problem is in progress.

Acknowledgment. We thank Allen Henderson for his assistance with the graphics and computing in the initial stage of development of this research. This work has been supported in part by the National Science Foundation, by the Air Force Office of Scientific Research, and by the Grant BIO96-0895 from CICYT (Spain) to F.M. During the realization of this work F.M. held a fellowship "Beca Complutense del Amo", Universidad Complutense de Madrid.

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