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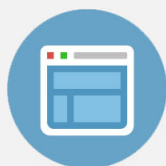
Nonlinear response theory in chemical kinetics

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A theory of nonlinear response of chemical kinetics, in which multiple perturbations are used to probe the time evolution of nonlinear chemical systems, is developed. Expressions for nonlinear chemical response functions and susceptibilities, which can serve as multidimensional measures of the kinetic pathways and rates, are derived. A new class of multidimensional measures that combine multiple perturbations and measurements is also introduced. Nonlinear fluctuation-dissipation relations for steady-state chemical systems, which replace operations of concentration measurement and perturbations, are proposed. Several applications to the analysis of complex reaction mechanisms are provided. © *2014 AIP Publishing LLC*. [http://dx.doi.org/10.1063/1.4861588]

I. INTRODUCTION

Great variety of problems in chemistry and biology involve complex reaction mechanisms.[1,2] These include elaborate reaction networks in combustion and atmospheric chemistry, complex enzyme catalyzed reactions in biology, protein networks in living cells and others. Analysis of the topology of complex reaction networks and their elementary steps require development of suitable experimental techniques.

In this paper we propose multidimensional time-dependent techniques, drawing upon the analogy with time-resolved nonlinear spectroscopy. In such experiments, the dynamical system of interest is subjected to a series of controlled external perturbations and its response is measured at a later time. The time intervals between the perturbations and the measurement constitute a multidimensional parameter space, which caries detailed information about the system. Multidimensional techniques are not normally applied for analysis of chemical kinetics, and this paper aims at extending the applicability of multidimensional methods of response to perturbations into the field of chemical kinetics.

Linear response experiments have been widely employed to study complex reaction mechanisms.[3–11] Nonlinear response of chemical systems have been also addressed,[12–16] mostly for one-dimensional, i.e., single-time nonlinear experiments, without resorting to multidimensional response signals. However, nonlinear signal of nth order implies response of a chemical system to n external perturbations, which can be applied and measured in n time intervals, and thus generally form an n-dimensional characterization of the chemical system. The nonlinearity comes from the kinetic equations describing time evolution of a chemical system, e.g., bimolecular reactions, catalyzed reactions, etc.

In the present paper, we show that nonlinear response functions formally similar to those of classical systems in phase space can be derived with minor modification for general nonlinear dynamical systems such as chemical reactions.

The canonical phase space structure is not essential. Similar to classical response theory in phase space, expressions of nonlinear chemical response functions contain stability derivatives, which potentially carry detailed dynamical information. We further show that fluctuation dissipation theorems can be derived for chemical systems out of equilibrium, e.g., steady states, provided they satisfy gaussian statistics.

The paper is organized as follows. In Sec. II, we present formal perturbative expressions for the nonlinear response of chemical systems. In Sec. III, we illustrate that the resulting perturbative series reproduce some exactly solvable problems in chemical kinetics. In Sec. IV, we consider several special forms of perturbations of chemical systems and obtain finite difference expressions for nonlinear response functions and susceptibilities. In Sec. V, we extend the class of nonlinear experiments to multiple perturbations and multiple measurements, and show that they carry complementary information to the nonlinear response functions. In Sec. VI, we derive approximate steady-state fluctuation-dissipation relations between the ordinary and generalized nonlinear response functions. In Sec. VII, we give several examples of the new information provided by multidimensional signals about the mechanisms of chemical reactions. The paper is concluded with discussion in Sec. VIII.

II. NONLINEAR RESPONSE OF A GENERAL DYNAMICAL SYSTEM

The time evolution of a general dynamical system can be described via a set of first order differential equations

$$\frac{dx_i}{dt} = h_i(\vec{x}, t), \qquad (2.1)$$

where x_i stands for the ith component of the N-dimensional vector $\vec{x}$ of dynamical variables. If higher order time derivatives are involved in the equations of motion, they still can be represented in the form of Eq. (2.1) by replacing higher order derivatives with new dynamical variables. The explicit time dependence of h_i in Eq. (2.1) implies variation of

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system's parameters with time. Examples of dynamical systems that can be described via Eq. (2.1) include:

(1) Chemical reactions,

$$\frac{dC_i}{dt} = -\sum_j k_j(t) C_1^{n_1} \dots C_N^{n_N}. \qquad (2.2)$$

(2) Classical Hamiltonian systems in phase space,

$$\frac{dx(t)}{dt} = p,$$
$$\frac{dp(t)}{dt} = -\frac{\partial V(x(t))}{\partial x}. \qquad (2.3)$$

(3) Currents in electric circuits,

$$\frac{dI}{dt} = -\frac{R(t)}{L} I, \qquad (2.4)$$

where R depends nonlinearly on I, and many others. While in this paper we will be mostly concerned with chemical systems, the results can be applied to a broader range of systems, whose time evolution is of the form in Eq. (2.1).

One of the most commonly used experimental approaches to study complex dynamical systems is to measure their response to a controlled external perturbation. For physical systems such perturbation could correspond to an externally applied force (such as laser pulse in optical spectroscopy), while for chemical systems it can correspond to a controlled change in concentration of a particular chemical species. Denoting a generalized external perturbation by $\delta h_i(\vec{x}, t)$, the equations of motion (2.1) become

$$\frac{dx_i}{dt} = h_i(\vec{x}, t) + \delta h_i(\vec{x}, t), \qquad (2.5)$$

where $h_i(\vec{x}, t)$ determines the unperturbed system's dynamics, usually at equilibrium or in a stationary state.

The measured quantities, $f(\vec{x})$, i.e., the observables, are some functions of the quantities being perturbed, x_i. Mathematically, we are interested in expressing the response of the observable $f(\vec{x})$ in terms of the imposed perturbation $\delta h_i(\vec{x}, t)$. This can be efficiently done using time dependent perturbation theory.[17–19] Since most derivations of time dependent perturbation theory are done for Hamiltonian systems, it will be instructive to provide a derivation for the general (non-Hamiltonian) dynamical system of the form in Eq. (2.5).

Let us consider an observable $f(\vec{x})$ which is an arbitrary differentiable function of coordinates $\vec{x}$. Since $df(\vec{x})/dt = \sum_j (\partial f(\vec{x})/\partial x_j)(dx_j(t)/dt)$, the evolution of $f(\vec{x}(t))$ is given by

$$\frac{df(\vec{x})}{dt} = (D_0(t) + \delta D(t)) f(\vec{x}), \qquad (2.6)$$

where the differential operators $D_0(t)$ and $\delta D(t)$ are

$$D_0(t) = \sum_{i=1}^{N} h_i(\vec{x}, t) \frac{\partial}{\partial x_i},$$
$$\delta D(t) = \sum_{i=1}^{N} \delta h_i(\vec{x}, t) \frac{\partial}{\partial x_i}. \qquad (2.7)$$

Here $\delta D(t)$ represents the combined effect of all perturbations at time t on the observable f. $\delta D(t)$ vanishes as the strength of perturbations δh_i goes to zero. We assume that initially the system is unperturbed, $\delta h_i|_{t=0} = 0$, and thus $\delta D(0) = 0$.

Equation (2.6) can be solved iteratively and its solution can be expressed in the known form[19]

$$f(\vec{x}(t)) = \mathcal{D}(t) f(\vec{x})|_{\vec{x}=\vec{x}(0)}, \qquad (2.8)$$

where we have introduced evolution (time translation) operator $\mathcal{D}(t)$,

$$\mathcal{D}(t) = T \exp \int_0^t D(\tau) d\tau$$
$$= 1 + \int_0^t D(\tau) d\tau + \int_0^t d\tau_2 \int_0^{\tau_2} d\tau_1 D(\tau_1) D(\tau_2) + \dots, \qquad (2.9)$$

with

$$D(t) \equiv D_0(t) + \delta D(t), \qquad (2.10)$$

and T represents the operation of time ordering. The evolution operator $\mathcal{D}(t)$ propagates the perturbed system in Eq. (2.6) forward in time, $\vec{x}(t) = \mathcal{D}(t)\vec{x}|_{\vec{x}=\vec{x}(0)}$. It is also useful to define evolution operator $\mathcal{D}_0(t) \equiv T \exp \int_0^t D_0(\tau) d\tau$ of the unperturbed system ($\delta D = 0$), which propagates the system along the unperturbed trajectories $\vec{x}_0(t)$, i.e.,

$$f(\vec{x}_0(t)) = \mathcal{D}_0(t) f(\vec{x}_0)|_{\vec{x}_0=\vec{x}(0)}. \qquad (2.11)$$

Since the initial conditions of the perturbed and unperturbed systems are the same, from Eqs. (2.8) and (2.11) one obtains the following relation between the observables along the perturbed and unperturbed trajectories,

$$f(\vec{x}(t)) = \mathcal{D}(t)\mathcal{D}_0^{-1}(t) f(\vec{x}_0(t)), \qquad (2.12)$$

where the differential operators $\mathcal{D}(t)$ and $\mathcal{D}_0^{-1}(t)$ act on the initial conditions $\vec{x}(0)$ which are common to both trajectories $\vec{x}(t)$ and $\vec{x}_0(t)$.

The differential operators $\mathcal{D}(t)$ and $\mathcal{D}_0(t)$ satisfy the following properties:[19]

$$\frac{d\mathcal{D}(t)}{dt} = \mathcal{D}(t) D(t),$$
$$\frac{d\mathcal{D}_0(t)}{dt} = \mathcal{D}_0(t) D_0(t), \qquad (2.13)$$
$$\frac{d\mathcal{D}_0^{-1}(t)}{dt} = -D_0(t)\mathcal{D}_0^{-1}(t),$$

where the last equation is obtained from $\frac{d}{dt}[\mathcal{D}_0(t)\mathcal{D}_0^{-1}(t)] = \frac{d}{dt} 1 = 0$, and all the differential operators in Eqs. (2.13) act at $\vec{x} = \vec{x}(0)$. Defining the product of differential operators in Eq. (2.12) with $S(t) \equiv \mathcal{D}(t)\mathcal{D}_0^{-1}(t)$ and using Eqs. (2.13)

one obtains the following differential equation for the operator $S(t)$,[17]

$$\frac{dS(t)}{dt} = S(t)\delta D_I(t),\qquad(2.14)$$

where

$$\delta D_I(t) \equiv \mathcal{D}_0(t)\delta D(t)\mathcal{D}_0^{-1}(t)\qquad(2.15)$$

can be considered as a perturbation operator in the classical interaction picture. From the definition of the operator $S(t)$ it follows that $S(0) = 1$, therefore integration of Eq. (2.14) gives

$$S(t) = 1 + \int_0^t d\tau\, S(\tau)\delta D_I(\tau).\qquad(2.16)$$

Iterative substitution of Eq. (2.16) into itself results in the following expansion for the operator $S(t)$:

$$S(t) = 1 + \int_0^t d\tau\,\delta D_I(\tau) + \int_0^t d\tau_2 \int_0^{\tau_2} d\tau_1 \delta D_I(\tau_1)\delta D_I(\tau_2)$$

$$+ \int_0^t d\tau_3 \int_0^{\tau_3} d\tau_2 \int_0^{\tau_2} d\tau_1 \delta D_I(\tau_1)\delta D_I(\tau_2)\delta D_I(\tau_3)\ldots.$$
$$(2.17)$$

Substituting Eq. (2.17) back into Eq. (2.12), one obtains the final expression for the response $f(\vec{x}(t))$ as a function of perturbation $\delta D_I(t)$ for a general (dynamical) system (2.5),

$$f(x(t)) = f(x_0(t)) + \int_0^t d\tau\,\delta D_I(\tau) f(x_0(t))$$

$$+ \int_0^t d\tau_2 \int_0^{\tau_2} d\tau_1 \delta D_I(\tau_1)\delta D_I(\tau_2) f(x_0(t)) + \ldots.$$
$$(2.18)$$

It is necessary to make a comment on the explicit form of the differential operators $\delta D_I(\tau)$ in Eq. (2.18) and the way they act to the right. Their action is explicitly given by

$$\delta D_I(\tau) f(x_0(t))$$
$$= \mathcal{D}_0(\tau)\delta D(\tau)\mathcal{D}_0^{-1}(\tau) f(x_0(t))$$
$$= \mathcal{D}_0(\tau)\left[\sum \delta h_i(\vec{x}(0), \tau)\frac{\partial}{\partial \vec{x}(0)}\right] f(x_0(t - \tau)).\quad(2.19)$$

Using the property of translation operators $Z = \mathcal{D}z$ from Ref. 20,

$$\mathcal{D}\left(\psi(z)\frac{\partial}{\partial z}\right) F(z) = \left(\psi(Z)\frac{\partial}{\partial Z}\right) F(Z),\qquad(2.20)$$

Eq. (2.19) results in

$$\delta D_I(\tau) f(x_0(t)) = \left[\sum \delta h_i(\vec{x}_0(\tau), \tau)\frac{\partial}{\partial \vec{x}_0(\tau)}\right] f(x_0(t)).$$
$$(2.21)$$

The latter implies that $\delta D_I(\tau)$ has the same form as $\delta D(\tau)$, in which, however, all the coordinates are taken at time τ along the unperturbed trajectory $\vec{x}_0(\tau)$, i.e., $\vec{x} = \vec{x}_0(\tau)$,

$$\delta D_I(\tau) = \sum \delta h_i(\vec{x}_0(\tau), \tau)\frac{\partial}{\partial \vec{x}_0(\tau)}.\qquad(2.22)$$

This form leads to the appearance of various stability derivatives $\partial x_0(t)/\partial x_0(\tau)$ in the expression (2.18). Such stability derivatives can be unbounded in time and may lead to the problems of divergence of nonlinear dynamical responses in systems with periodic[21,22] and chaotic Hamiltonian dynamics.[23] In some cases the latter divergence problem can be eliminated by canonical averaging[24] or in strongly chaotic[25,26] systems. It is expected that stability derivatives of chemical kinetics do not diverge in time due to the generally stable dynamic behavior of mass-action systems,[27,28] and thus should not lead to unphysical time growth of their dynamical response.

Expression (2.18) serves as a unified nonlinear response theory of any dynamical system, e.g., chemical kinetics. It is instructive to show that Eq. (2.18) reduces to the well-known expression of classical response for Hamiltonian systems. Indeed, for a system with a Hamiltonian $H_0(p, x)$ perturbed by external field $E(t)$ and interaction energy $\delta H = \mu(p, x)E(t)$, its equations of motion read

$$\frac{dx}{dt} = \frac{\partial H_0}{\partial p} + \frac{\partial \mu}{\partial p}E(t),$$
$$\frac{dp}{dt} = -\frac{\partial H_0}{\partial x} - \frac{\partial \mu}{\partial x}E(t).$$
$$(2.23)$$

From Eqs. (2.23), the corresponding perturbation operator in Eq. (2.22) is

$$\delta D_I(t)$$
$$= E(t)\left[\frac{\partial \mu(x_0(t), p_0(t))}{\partial p_0(t)}\frac{\partial}{\partial x_0(t)} - \frac{\partial \mu(x_0(t), p_0(t))}{\partial x_0(t)}\frac{\partial}{\partial p_0(t)}\right]$$
$$= -E(t)\{\ldots, \mu_0(t)\},\qquad(2.24)$$

where $\mu_0(t) \equiv \mu(x_0(t), p_0(t))$ and $\{\ldots, \ldots\}$ is the Poisson bracket operation $\{A, B\} = \frac{\partial A}{\partial x_0}\frac{\partial B}{\partial p_0} - \frac{\partial A}{\partial p_0}\frac{\partial B}{\partial x_0}$. The observable measured in optical response theory is the dipole moment $\mu(x(t), p(t))$, which from Eq. (2.18) has the following form:

$$\mu(x(t), p(t)) = \mu_0(t) - \int_0^t d\tau\, E(\tau)\{\mu_0(t), \mu_0(\tau)\}$$

$$+ \int_0^t d\tau_2 \int_0^{\tau_2} d\tau_1 E(\tau_2)E(\tau_1)\{\{\mu_0(t), \mu_0(\tau_2)\},$$
$$\mu_0(\tau_1)\} + \ldots.\qquad(2.25)$$

When the dipole moment $\mu(x(t), p(t))$ in Eq. (2.25) is averaged over equilibrium initial conditions, $\langle\mu(x(t), p(t))\rangle$, the multi-point averages under the integrals can be identified as the nonlinear response functions[29] $(-1)^n \langle\{\ldots\{\mu_0(t), \mu_0(\tau_n)\}, \ldots \mu_0(\tau_1)\}\rangle$.

III. APPLICATION OF NONLINEAR RESPONSE THEORY TO CHEMICAL KINETICS

Equation (2.18) can be used to predict the linear or nonlinear responses of chemical systems to perturbations involving the concentrations of substances. In this section, we illustrate the application of Eq. (2.18) to several exactly solvable problems of chemical kinetics.

A. Perturbation of first order kinetics (unimolecular reaction)

Consider a first-order chemical reaction

$$\frac{dC}{dt} = -k(t)C + F(t), \tag{3.1}$$

where $F(t)$ is some external perturbation and $C(0) = c_0$ is the initial condition. If the observable of interest is the concentration C, then the parameters entering Eq. (2.18) are

$$f(C) = C, \tag{3.2a}$$

$$x_0(t) \equiv C_0(t) = c_0 e^{-\int_0^t k(t)dt}, \tag{3.2b}$$

$$\delta D_I(t) = F(t)\frac{\partial}{\partial C_0(t)}. \tag{3.2c}$$

Substituting Eqs. (3.2a)–(3.2c) into Eq. (2.18) one gets the following solution of Eq. (3.1):

$$C(t) = C_0(t) + \int d\tau F(\tau)\frac{\partial C_0(t)}{\partial C_0(\tau)}$$
$$= C_0(t) + \int d\tau F(\tau)e^{-\int_\tau^t k(t)dt}. \tag{3.3}$$

This coincides with the well-known exact solution of Eq. (3.1),

$$C(t) = c_0 e^{-\int_0^t k(t)dt} + \int d\tau F(\tau)e^{-\int_\tau^t k(t)dt}. \tag{3.4}$$

Since higher order derivatives $\partial^n C_0(t)/\partial C_0(\tau_1)\ldots\partial C_0(\tau_n)$, $n \geq 2$, vanish for the unperturbed solution $C_0(t)$ in Eq. (3.2b), higher order terms in powers of $F(t)$ in Eq. (3.3) do not appear, therefore no nonlinear response exists for a first order chemical reaction with a linear observable $f(C) = C$; the system is strictly linear.

It is also instructive to check by direct evaluation of Eq. (2.18) that the time evolution of the observable $f(C) = C^2$,

$$C(t)^2 = C_0(t)^2 + 2C_0(t)\int d\tau_1 F(\tau_1)e^{-\int_{\tau_1}^t k(\tau)d\tau}$$
$$+ 2\int_0^t d\tau_2 F(\tau_2)e^{-\int_{\tau_2}^t k(\tau)d\tau}\int_0^{\tau_2} d\tau_1 F(\tau_1)e^{-\int_{\tau_1}^t k(\tau)d\tau} \tag{3.5}$$

again coincides with the exact solution, i.e., squared Eq. (3.4). One should keep in mind when making the latter comparison that the time-ordered integral $\int_0^t d\tau_2 \int_0^{\tau_2} d\tau_1 f(\tau_2)f(\tau_1)$ is exactly one half of the full time domain integral $\int_0^t d\tau_2 \int_0^t d\tau_1 f(\tau_2)f(\tau_1)$.

B. Perturbation of second order kinetics (bimolecular reactions)

Another exactly solvable kinetic scheme is a bimolecular reaction

$$\frac{dC}{dt} = -k(t)C^2 + F(t)C. \tag{3.6}$$

The perturbation is taken to be of the form $F(t)C$ only to make the kinetic equation the same as exactly solvable Bernoulli equation. The unperturbed solution $C_0(t)$ is

$$\frac{1}{C_0(t)} = \frac{1}{c_0} + \int_0^t k(\tau)d\tau, \tag{3.7}$$

and the exact solution $C(t)$ of the perturbed equation, i.e., Bernoulli equation, is

$$\frac{1}{C(t)} = \frac{1}{c_0}e^{-\int_0^t F(\tau)d\tau} + e^{-\int_0^t F(\tau)d\tau}\int_0^t e^{\int_0^{\tau'} F(\tau)d\tau}k(\tau')d\tau'. \tag{3.8}$$

We now apply Eq. (2.18) to obtain perturbative solution of Eq. (3.6). In this case, the corresponding operator of perturbation is $\delta D_I(t) = F(t)C_0(t)\partial/\partial C_0(t)$. Using the perturbation theory result (2.18) for an observable $f(C) = 1/C$, we obtain

$$\frac{1}{C(t)} = \frac{1}{C_0(t)} + \int_0^t d\tau_1 F(\tau_1)C_0(\tau_1)\frac{\partial}{\partial C_0(\tau_1)}\frac{1}{C_0(t)}$$
$$+ \int_0^t d\tau_2 \int_0^{\tau_2} d\tau_1 F(\tau_2)F(\tau_1)C_0(\tau_1)\frac{\partial}{\partial C_0(\tau_1)}C_0(\tau_2)$$
$$\times \frac{\partial}{\partial C_0(\tau_2)}\frac{1}{C_0(t)} + \ldots$$
$$= \frac{1}{C_0(t)} - \frac{1}{c_0}\int_0^t F(\tau)d\tau - \int_0^t k(\tau)d\tau\int_\tau^t F(\tau_1)d\tau_1$$
$$+ \frac{1}{c_0}\int_0^t d\tau_2 \int_0^{\tau_2} d\tau_1 F(\tau_2)F(\tau_1) + \int_0^t d\tau\int_\tau^t d\tau_2$$
$$\times \int_\tau^{\tau_2} d\tau_1 F(\tau_2)F(\tau_1)k(\tau) + \ldots. \tag{3.9}$$

This coincides with the Taylor expansion of the exact solution in Eq. (3.8) in powers of $F(t)$.

IV. SPECIAL TYPES OF PERTURBATIONS

We now examine two particular cases of perturbations that can be used to probe chemical systems.

A. Impulsive perturbation

The simplest way to perturb a chemical system is to instantaneously add a small amount of ith chemical species (it is assumed that chemical system is well stirred and that the system is homogeneous). This corresponds to impulsive increase in concentration of species i by some amount Δc_i and results in the following kinetic scheme:

$$\frac{dC_j}{dt} = g_j(\vec{C}, t) + \Delta c_i \delta_{ij}\delta(t - t_1), \tag{4.1}$$

where δ_{ij} is the Kronecker symbol and $\delta(t - t_1)$ is Dirac delta-function that represents impulsive perturbation at time t_1. The perturbation operator $\delta D_I(t)$ corresponding to the system of differential equations (4.1) is

$$\delta D_I(t) = \Delta c_i \delta(t - t_1)\frac{\partial}{\partial C_{0i}(t)}$$
$$= \Delta c_i \delta(t - t_1)C_{0i}^-(t), \tag{4.2}$$

where $\vec{C}_0(t)$ is a solution of the unperturbed system of equations $dC_i/dt = g(\vec{C}, t)$, and we have defined the operator $C_{0i}^-(t) \equiv \partial/\partial C_{0i}(t)$ to simplify further notation.

At later times after the perturbation, one can measure the concentration $C_j(t)$ of a species j, i.e., a response of the chemical system. $C_j(t)$ is given in Eq. (2.18) and reads

$$C_j(t) = C_{0j}(t) + \Delta c_i C_{0i}^-(t_1) C_{0j}(t)$$
$$+ \frac{1}{2} \Delta c_i^2 C_{0i}^-(t_1) C_{0i}^-(t_1) C_{0j}(t) + \dots . \quad (4.3)$$

If a set of experiments are performed at various initial conditions, or if the chemical system fluctuates, the quantity C_j should be replaced with its average over initial conditions $\langle C_j(t) \rangle = \int d\vec{C}(0) \rho(\vec{C}(0)) C_j(t)$,

$$\langle C_j(t) \rangle = \langle C_{0j}(t) \rangle + \Delta c_i \langle C_{0i}^-(t_1) C_{0j}(t) \rangle$$
$$+ \frac{1}{2} \Delta c_i^2 \langle C_{0i}^-(t_1) C_{0i}^-(t_1) C_{0j}(t) \rangle + \dots . \quad (4.4)$$

We note that the right side of Eq. (4.4) contains multipoint averages which are functions of the solution $\vec{C}_0(t)$ of the *unperturbed* system and can therefore serve as multidimensional characteristics of the unperturbed system. In Hamiltonian systems, these quantities are called *response functions*, and we will adopt the same terminology for chemical kinetics. These response functions can be measured experimentally. For instance, the "linear" response function $\langle C_{0i}^-(t_0) C_{0j}(t) \rangle$ can be obtained from Eq. (4.4) (or measured in experiments with single impulsive perturbation at time t_1) as

$$\langle C_{0i}^-(t_1) C_{0j}(t) \rangle = \left. \frac{\partial}{\partial(\Delta c_i)} \langle C_j(t) \rangle \right|_{\Delta c_i = 0}. \quad (4.5)$$

Similarly, the higher order, "nonlinear," response functions $\langle C_{0i}^-(t_1) C_{0n}^-(t_2) C_{0j}(t) \rangle$ can be obtained from experiments with two consecutive perturbations: first, of concentration of species i at time t_1, second, of species n at time t_2, and a measurement of concentration of species j at time t,

$$\frac{dC_j}{dt} = g_j(\vec{C}, t) + \Delta c_i \delta_{ij} \delta(t - t_1) + \Delta c_n \delta_{nj} \delta(t - t_2),$$
$$(4.6)$$

and thus from Eq. (2.18) one can find

$$\langle C_{0i}^-(t_1) C_{0n}^-(t_2) C_{0j}(t) \rangle = \left. \frac{\partial^2}{\partial(\Delta c_i)\partial(\Delta c_n)} \langle C_j(t) \rangle \right|_{\Delta c_i, \Delta c_n = 0}. \quad (4.7)$$

The k-point response functions $\langle C_{0i}^-(t_1) \dots C_{0n}^-(t_{k-1}) C_{0j}(t) \rangle$ depend on $k - 1$ time intervals $t - t_{k-1}, \dots t_2 - t_1$, and thus can serve as $k - 1$-dimensional dynamic measures of the unperturbed chemical system under study. The latter provides additional tools for exploring the (unknown) behavior of $\vec{C}_0(t)$ and thus the reaction topology and its kinetic parameters. In Sec. V, we expand the class of these multidimensional measures even further by introducing generalized response functions that correspond to experiments that combine multiple perturbations and multiple measurements.

B. Oscillatory perturbations

Another way to perturb a chemical system is to change one of its control parameters (or several parameters) periodically. For instance, if a chemical system reaches a steady state with a constant influx j_i of species i, one can modulate this flux by adding an oscillatory component $\delta j_i(t) = \epsilon \cos(\Omega t)$. Another example: if the concentration of species i is held constant by buffering, $C_i = \text{const}$, one can modulate this concentration by adding an oscillatory perturbation. General kinetic scheme corresponding to oscillatory perturbation can be written as

$$\frac{dC_j}{dt} = g_j(\vec{C}, t) + \epsilon h_j(\vec{C}) \cos(\Omega_1 t). \quad (4.8)$$

The perturbation operator corresponding to Eq. (4.8) is

$$\delta D(t) = \epsilon \cos(\Omega_1 t) \sum_j h_j(\vec{C}(0)) \frac{\partial}{\partial C_j(0)}$$
$$\equiv \epsilon \cos(\Omega_1 t) V_-. \quad (4.9)$$

Using Eq. (2.18), one can expand an observable concentration $C_j(t)$ in a perturbative series

$$C_j(t) = C_{0j}(t) + \epsilon \int_0^t d\tau \, \mathcal{D}_0(\tau) V_- \mathcal{D}_0^{-1}(\tau) \mathcal{D}_0(t) C_{0j}(0) \cos(\Omega_1 \tau)$$
$$+ \epsilon^2 \int_0^t d\tau_2 \int_0^{\tau_2} d\tau_1 \, \mathcal{D}_0(\tau_1) V_- \mathcal{D}_0^{-1}(\tau_1) \mathcal{D}_0(\tau_2) V_- \mathcal{D}_0^{-1}(\tau_2)$$
$$\times \mathcal{D}_0(t) C_{0j}(0) \cos(\Omega_1 \tau_1) \cos(\Omega_1 \tau_2) + \dots . \quad (4.10)$$

Averaging Eq. (4.10) over stationary initial conditions and using the property of invariance of trace under time shift $\text{Tr}[\rho(C(0)) \mathcal{D}_0(\tau) f] = \text{Tr}[\mathcal{D}_0^{-1}(\tau) \rho(C(0)) \mathcal{D}_0(\tau) f]$ as well the property of invariance of stationary distribution density with respect to time shift $\text{Tr}[\mathcal{D}_0^{-1}(\tau) \rho(C(0)) \mathcal{D}_0(\tau) f]$ $= \text{Tr}[\rho(C_0(-\tau)) f] = \text{Tr}[\rho(C_0(0)) f]$, Eq. (4.10) can be simplified

$$\langle C_j(t) \rangle = \langle C_{0j}(t) \rangle + \epsilon \int_0^t d\tau \langle V_- \mathcal{D}_0(t - \tau) C_{0j}(0) \rangle \cos(\Omega_1 \tau)$$
$$+ \epsilon^2 \int_0^t d\tau_2 \int_0^{\tau_2} d\tau_1 \langle V_- \mathcal{D}_0(\tau_2 - \tau_1) V_- \mathcal{D}_0(t - \tau_2)$$
$$\times C_{0j}(0) \rangle \cos(\Omega_1 \tau_1) \cos(\Omega_1 \tau_2) + \dots . \quad (4.11)$$

Taking Fourier transform of Eq. (4.10), one gets

$$\langle \widetilde{C}_j(\omega) \rangle = \langle \widetilde{C}_{0j}(\omega) \rangle$$
$$+ \epsilon \int d\omega_1 \delta(\omega - \omega_1) \langle V_- \widetilde{\mathcal{D}}_0(\omega_1) C_{0j}(0) \rangle$$
$$\times \pi \left(\delta(\omega_1 - \Omega_1) + \delta(\omega_1 + \Omega_1) \right)$$
$$+ \frac{\epsilon^2}{2\pi} \int d\omega_1 \int d\omega_2 \delta(\omega - \omega_1 - \omega_2)$$
$$\times \langle V_- \widetilde{\mathcal{D}}_0(\omega_1) V_- \widetilde{\mathcal{D}}_0(\omega_1 + \omega_2) C_{0j}(0) \rangle$$
$$\times \pi^2 \left(\delta(\omega_1 - \Omega_1) + \delta(\omega_1 + \Omega_1) \right) \left(\delta(\omega_2 - \Omega_1) \right.$$
$$\left. + \delta(\omega_2 + \Omega_1) \right) + \dots . \quad (4.12)$$

Defining nonlinear susceptibilities $\chi^{(n)}(\omega_1, \ldots \omega_2)$,

$$\langle \widetilde{C}_j(\omega) \rangle = \langle \widetilde{C}_{0j}(\omega) \rangle$$
$$+ \sum_n \frac{1}{(2\pi)^{n-1}} \int d\omega_1 \ldots \int d\omega_n \delta(\omega - \omega_1 - \ldots - \omega_n)$$
$$\times \chi^{(n)}(\omega_1, \ldots, \omega_n) \widetilde{F}(\omega_1) \ldots \widetilde{F}(\omega_n), \qquad (4.13)$$

with $F(t) = \epsilon \cos(\Omega_1 t)$, Eq. (4.12) provides a way to measure these quantities:

$$\chi^{(1)}(\Omega_1) \equiv \langle V_- \widetilde{\mathcal{D}}_0(\Omega_1) C_{0j}(0) \rangle$$
$$= \frac{1}{\pi} \frac{\partial}{\partial \epsilon} \left[\int_{\Omega_1 - \Delta\Omega}^{\Omega_1 + \Delta\Omega} \langle \widetilde{C}_j(\omega) \rangle d\omega \right]_{\epsilon=0}, \qquad (4.14a)$$

$$\chi^{(2)}(\Omega_1, \Omega_1) \equiv \langle V_- \widetilde{\mathcal{D}}_0(\Omega_1) V_- \widetilde{\mathcal{D}}_0(2\Omega_1) C_{0j}(0) \rangle$$
$$= \frac{1}{2\pi} \frac{\partial^2}{\partial \epsilon^2} \left[\int_{2\Omega_1 - \Delta\Omega}^{2\Omega_1 + \Delta\Omega} \langle \widetilde{C}_j(\omega) \rangle d\omega \right]_{\epsilon=0}. \qquad (4.14b)$$

Similarly, for a perturbation with two frequencies, $F(t) = \epsilon_1 \cos(\Omega_1 t) + \epsilon_2 \cos(\Omega_2 t)$, one gets

$$\chi^{(2)}(\Omega_1, \Omega_2) \equiv \langle V_- \widetilde{\mathcal{D}}_0(\Omega_1) V_- \widetilde{\mathcal{D}}_0(\Omega_1 + \Omega_2) C_{0j}(0) \rangle$$
$$+ \langle V_- \widetilde{\mathcal{D}}_0(\Omega_2) V_- \widetilde{\mathcal{D}}_0(\Omega_1 + \Omega_2) C_{0j}(0) \rangle,$$

$$= \frac{1}{\pi} \frac{\partial^2}{\partial \epsilon_1 \partial \epsilon_2} \left[\int_{\Omega_1 + \Omega_2 - \Delta\Omega}^{\Omega_1 + \Omega_2 + \Delta\Omega} \langle \widetilde{C}_j(\omega) \rangle d\omega \right]_{\epsilon_1=0, \epsilon_2=0}. \qquad (4.15)$$

In general, the nth order nonlinear susceptibility can be obtained from the experiment with $F(t) = \sum_{i=1}^{n} \epsilon_i \cos(\Omega_i t)$ as follows:

$$\chi^{(n)}(\Omega_1, \ldots, \Omega_n)$$
$$= \frac{1}{\pi} \frac{\partial^n}{\partial \epsilon_1 \ldots \partial \epsilon_n} \left[\int_{\Omega_1 + \ldots + \Omega_n - \Delta\Omega}^{\Omega_1 + \ldots \Omega_n + \Delta\Omega} \langle \widetilde{C}_j(\omega) \rangle d\omega \right]_{\epsilon_1=0, \ldots, \epsilon_n=0}, \qquad (4.16)$$

where the integral on the right side is taken over an interval $(\Omega_0 - \Delta\Omega, \Omega_0 + \Delta\Omega)$ in the vicinity of the peak at $\omega = \Omega_0 = \Omega_1 + \ldots + \Omega_n$.

Similar to the time domain chemical nonlinear response functions discussed in Subsection IV A, the nonlinear susceptibilities constitute n-dimensional frequency-domain measures of the unperturbed kinetics $\vec{C}_0(t)$. The only difference, however, is that perturbations in nonlinear response functions are ordered in time, while in nonlinear susceptibilities they are not. We also note that in some cases Laplace transform may be used instead of Fourier transform to more clearly represent non-oscillating exponential signal decays.

V. GENERALIZED RESPONSE FUNCTIONS: COMBINING MULTIPLE PERTURBATIONS AND MEASUREMENTS

In Secs. II– IV, we have introduced response functions which can serve as multidimensional *causal* measures of chemical kinetics. The nth order response function depends on n time intervals (thus being an n-dimensional measure) and corresponds to experiment consisting of n perturbations of a chemical system followed by a single measurement of concentration of some species. However, this class of multidimensional measures can be extended even further, by introducing a new type of experiments which combine multiple perturbations and measurements.[30,31] Indeed, one can perturb a chemical system k times while measuring concentrations m times between or after perturbations to result in $k + m$ dimensional measure. We now examine what new information can be extracted from this type of experiments.

Suppose the concentration of species i is impulsively increased by Δc_i at time t_1, after which the concentration of species j is measured at time t_2 and the concentration of species l is measured at time t_3. From the latter two measurements one can construct a correlation function $\langle C_j(t_2) C_l(t_3) \rangle$. Using the perturbative expansion in Eq. (2.18), one can express the concentrations $C_j(t_2)$ and $C_l(t_3)$ as

$$C_j(t_2) = C_{0j}(t_2) + \Delta c_i C_{0i}^-(t_1) C_{0j}(t_2) + O(\Delta c_i^2)$$
$$C_l(t_3) = C_{0l}(t_3) + \Delta c_i C_{0i}^-(t_1) C_{0l}(t_3) + O(\Delta c_i^2), \qquad (5.1)$$

which leads to

$$\langle C_j(t_2) C_l(t_3) \rangle$$
$$= \langle C_{0j}(t_2) C_{0l}(t_3) \rangle + \Delta c_i \langle C_{0j}(t_2) C_{0i}^-(t_1) C_{0l}(t_3) \rangle$$
$$+ \Delta c_i \langle C_{0l}(t_3) C_{0i}^-(t_1) C_{0j}(t_2) \rangle + O(\Delta c_i^2)$$
$$= \langle C_{0j}(t_2) C_{0l}(t_3) \rangle + \Delta c_i \langle C_{0i}^-(t_1) C_{0j}(t_2) C_{0l}(t_3) \rangle + O(\Delta c_i^2). \qquad (5.2)$$

Equation (5.2) implies that the following quantity can be extracted using an experiment involving one perturbation and two measurements

$$\langle C_{0i}^-(t_1) C_{0j}(t_2) C_{0l}(t_3) \rangle = \frac{d}{d(\Delta c_i)} \langle C_j(t_2) C_l(t_3) \rangle \bigg|_{\Delta c_i = 0}. \qquad (5.3)$$

The object on the left side of Eq. (5.3) is a new quantity that depends on two time intervals, $t_2 - t_1$, $t_3 - t_2$, and is determined by time evolution $\vec{C}_0(t)$ of the unperturbed chemical system. Thus, this object can serve as an *additional* two-dimensional measure of the chemical kinetics $\vec{C}_0(t)$ under study.

One can notice a similarity between the two-dimensional measures in Eqs. (5.3) and (4.7) and note that the operation of perturbation corresponds to the time-dependent operator $C_0^-(t)$, while the operation of measurement corresponds to $C_0(t)$. It is therefore easy to write down all possible two-dimensional measures that can be obtained from other experiments with multiple perturbations and measurement. For instance, an experiment consisting of a measurement at t_1,

perturbation at t_2 and measurement at t_3 will produce the following quantity:

$$\langle C_{0j}(t_1)C_{0i}^-(t_2)C_{0l}(t_3)\rangle = \frac{d}{d(\Delta c_i)}\langle C_j(t_1)C_l(t_3)\rangle\bigg|_{\Delta c_i=0}. \tag{5.4}$$

In Ref. 30, we called these new quantities generalized response functions. Overall, there are 2^n generalized response functions that depend on n time intervals. For instance, for $n = 3$, the following 8 quantities can be obtained in 8 type of experiments with k perturbations and m measurements ($k + m = 4$),

$$\langle C_{0i}(t_1)C_{0j}(t_2)C_{0l}(t_3)C_{0p}(t_4)\rangle; \langle C_{0i}(t_1)C_{0j}(t_2)C_{0l}^-(t_3)C_{0p}(t_4)\rangle;$$

$$\langle C_{0i}(t_1)C_{0j}^-(t_2)C_{0l}(t_3)C_{0p}(t_4)\rangle; \langle C_{0i}^-(t_1)C_{0j}(t_2)C_{0l}(t_3)C_{0p}(t_4)\rangle;$$

$$\langle C_{0i}^-(t_1)C_{0j}^-(t_2)C_{0l}(t_3)C_{0p}(t_4)\rangle; \langle C_{0i}^-(t_1)C_{0j}(t_2)C_{0l}^-(t_3)C_{0p}(t_4)\rangle;$$

$$\langle C_{0i}(t_1)C_{0j}^-(t_2)C_{0l}^-(t_3)C_{0p}(t_4)\rangle; \langle C_{0i}^-(t_1)C_{0j}^-(t_2)C_{0l}^-(t_3)C_{0p}(t_4)\rangle,$$

where the first quantity is a 4-point ordinary correlation function and the last quantity is the 3rd order ordinary response function. All of these quantities carry different complementary information about the unperturbed chemical system and can thus be used as convenient probes of reaction topology and kinetics. In Sec. VII, we will demonstrate what information generalized response functions can provide and how they can be used to uncover the topology of complex reaction networks.

Similar to the discussion in Sec. IV B, one can also define generalized frequency-domain susceptibilities $\chi^{(m,k)}$,

$$\langle \widetilde{C}_1(\omega_1)\ldots\widetilde{C}_m(\omega_m)\rangle$$
$$= \langle \widetilde{C}_{01}(\omega_1)\ldots\widetilde{C}_{0m}(\omega_m)\rangle$$
$$+ \sum_n \frac{1}{(2\pi)^{n-1}}\int d\omega_1'\ldots\int d\omega_k'\delta(\omega_1+\ldots$$
$$+\omega_m-\omega_1'-\ldots-\omega_k')$$
$$\times \chi^{(m,k)}(\omega_1,\ldots,\omega_m,\omega_1',\ldots,\omega_k')\widetilde{F}(\omega_1')\ldots\widetilde{F}(\omega_k'), \tag{5.5}$$

each corresponding to k perturbations on frequencies $\omega_1',\ldots,\omega_k'$ and $m = n - k + 1$ measurements on frequencies $\omega_1,\ldots,\omega_m$.

VI. FLUCTUATION-DISSIPATION RELATIONS FOR GAUSSIAN STATISTICS

In Sec. V, we have shown that one can construct various kinds of experiments with m perturbations and $k = n - m + 1$ measurements to obtain 2^n different n-dimensional measures of dynamics of the chemical system of interest. However, in Ref. 30 we have shown, that in case of systems with thermal a Boltzmann distribution, only n of them will actually be independent, since there exist $2^n - n$ generalized fluctuation-dissipation relations connecting these quantities. In chemical kinetics, however, the reference state is not thermal equilibrium but instead a steady-state. Fluctuation-dissipation rela-

tions in systems at steady-state are not trivial even for the linear case.[32] Nevertheless, they can have a simple form if the distribution function of system's variables can be approximated with a Gaussian.

Consider a general kinetic scheme

$$\frac{dC_j}{dt} = g_j(\vec{C}, t), \tag{6.1}$$

which can reach a steady state. In a finite size open chemical system the number of molecules of species i can vary due to molecules coming and leaving the reactor cell. The uncertainty in the number of molecules results in a finite-size stationary distribution density $\rho(\vec{C})$, which can be approximated with a Gaussian using the central limit theorem

$$\rho(\vec{C}) = A\prod_{i=1}^N \exp\left(-\frac{(C_i - C_i^\mu)^2}{2\sigma_i^2}\right), \tag{6.2}$$

where σ_i^2 and C_i^μ are the variance and the mean of C_i. Considering Eq. (6.2) as distribution function for the initial conditions, one can derive fluctuation-dissipation-type relations for the generalized response functions. For instance, in case of first-order chemical response function, one has

$$\langle C_{0i}^-(0)C_{0j}(t)\rangle = \int d\vec{C}(0)A\prod_{j=1}^N \exp\left(-\frac{(C_j(0) - C_j^\mu)^2}{2\sigma_j^2}\right)$$
$$\times \frac{\partial}{\partial C_{0i}(0)}C_{0j}(t)$$
$$= \int d\vec{C}(0)A\prod_{j=1}^N \exp\left(-\frac{(C_j(0) - C_j^\mu)^2}{2\sigma_j^2}\right)$$
$$\times \frac{(C_{0i}(0) - C_i^\mu)}{\sigma_i^2}C_{0j}(t)$$
$$= \frac{1}{\sigma_i^2}\langle C_{0i}(0)C_{0j}(t)\rangle - \frac{C_i^{\mu 2}}{\sigma_i^2}, \tag{6.3}$$

where integration by parts was used in the second step.

Similarly, for nonlinear two-dimensional generalized response functions one obtains the following relations:

$$\langle C_{0i}^-(0)C_{0j}(t_1)C_{0l}(t_2)\rangle = \frac{1}{\sigma_i^2}\langle C_{0i}(0)C_{0j}(t_1)C_{0l}(t_2)\rangle$$
$$- \frac{C_i^\mu}{\sigma_i^2}\langle C_{0j}(t_1)C_{0l}(t_2)\rangle,$$
$$\langle C_{0i}^-(0)C_{0j}^-(t_1)C_{0l}(t_2)\rangle = \frac{1}{\sigma_i^2}\langle C_{0i}(0)C_{0j}^-(t_1)C_{0l}(t_2)\rangle$$
$$- \frac{C_i^\mu}{\sigma_i^2}\langle C_{0j}^-(t_1)C_{0l}(t_2)\rangle, \tag{6.4}$$

and for three-dimensional generalized response functions, one gets

$$\langle C_{0i}^-(0)C_{0j}(t_1)C_{0l}(t_2)C_{0p}(t_3)\rangle$$
$$= \frac{1}{\sigma_i^2}\langle C_{0i}(0)C_{0j}(t_1)C_{0l}(t_2)C_{0p}(t_3)\rangle$$
$$- \frac{C_i^\mu}{\sigma_i^2}\langle C_{0j}(t_1)C_{0l}(t_2)C_{0p}(t_3)\rangle,$$

$$\langle C_{0i}^-(0)C_{0j}^-(t_1)C_{0l}(t_2)C_{0p}(t_3)\rangle$$
$$= \frac{1}{\sigma_i^2}\langle C_{0i}(0)C_{0j}^-(t_1)C_{0l}(t_2)C_{0p}(t_3)\rangle$$
$$- \frac{C_i^\mu}{\sigma_i^2}\langle C_{0j}^-(t_1)C_{0l}(t_2)C_{0p}(t_3)\rangle,$$

$$\langle C_{0i}^-(0)C_{0j}^-(t_1)C_{0l}^-(t_2)C_{0p}(t_3)\rangle$$
$$= \frac{1}{\sigma_i^2}\langle C_{0i}(0)C_{0j}^-(t_1)C_{0l}^-(t_2)C_{0p}(t_3)\rangle \qquad (6.5)$$
$$- \frac{C_i^\mu}{\sigma_i^2}\langle C_{0j}^-(t_1)C_{0l}^-(t_2)C_{0p}(t_3)\rangle,$$

$$\langle C_{0i}(0)C_{0j}(t_1)C_{0l}^-(t_2)C_{0p}(t_3)\rangle$$
$$= \frac{1}{\sigma_i^2}\langle C_{0i}(0)C_{0j}(t_1)C_{0l}^-(t_2)C_{0p}(t_3)\rangle$$
$$- \frac{C_i^\mu}{\sigma_i^2}\langle C_{0j}(t_1)C_{0l}^-(t_2)C_{0p}(t_3)\rangle,$$

$$\langle C_{0i}(0)C_{0j}^-(t_1)C_{0l}(t_2)C_{0p}(t_3)\rangle$$
$$= \frac{1}{\sigma_j^2}\langle C_{0i}(0)C_{0j}(t_1)C_{0l}(t_2)C_{0p}(t_3)\rangle$$
$$- \frac{C_j^\mu}{\sigma_j^2}\langle C_{0j}(t_1)C_{0l}(t_2)C_{0p}(t_3)\rangle$$
$$- \langle C_{0p}(t_3)C_{0l}(t_2)C_{0j}^-(t_1)C_{0i}(0)\rangle.$$

When the concentration of the same species is perturbed and measured, i.e., $i = j = l = \ldots = p$ there should be at least n independent generalized response functions due to the n independent stability derivatives $\partial^k C_0(t)/\partial C_0(t_1)\ldots \partial C_0(t_k)$, $k = 0$, $\ldots$, $n - 1$ appearing the expressions of GRFs.

It is interesting to note that fluctuation-dissipation relations provide an opportunity to replace some measurement operations with perturbations. This has an important practical aspect, since in chemical systems it may be difficult to measure concentrations of particular species, while it can be straightforward to perturb them.

VII. INFORMATION CONTAINED IN MULTIDIMENSIONAL SIGNALS

The ordinary and generalized nonlinear response functions and susceptibilities, introduced in Secs. II– VI, are multidimensional characteristics (measures) of complex reaction kinetics and contain valuable information on the mechanism and connectivity of chemical reactions.

Below we present two examples of what extra information can be obtained from multidimensional signals as compared to one-dimensional techniques. We consider two experiments which provide two different two-dimensional measures: (1) a second-order nonlinear response experiment in which a chemical system is subjected to 2 perturbations and 1 measurement, and (2) a generalized second-order response experiment, introduced in Sec. V, in which a chemical system is subjected to 1 perturbation and 2 measurements at later times. As discussed in Secs. II– VI, these two-dimensional measures can be obtained either in time domain or in frequency domain. For the purpose of illustration we consider the first experiment in the frequency domain, and the second in the time domain.

A. Multidimensional frequency domain signal

Consider a one-variable nonlinear kinetic scheme

$$\frac{dx}{dt} = f(x, \epsilon), \qquad (7.1)$$

where x is a substance concentration and ϵ is a system's parameter, which can be perturbed. This kinetic scheme corresponds, for instance, to a Schlögl model[14,33]

$$A + X \underset{k_2}{\overset{k_1}{\rightleftarrows}} 2X,$$
$$X \underset{k_4}{\overset{k_3}{\rightleftarrows}} B, \qquad (7.2)$$
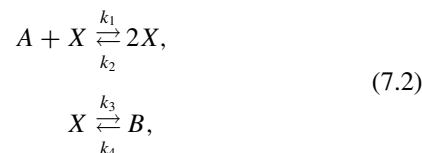
where the concentrations of A and B are kept constant and act as control parameters (i.e., $\epsilon = [A]$ or $\epsilon = [B]$),

$$\frac{d[X]}{dt} = -k_2[X]^2 + k_1[A][X] - k_3[X] + k_4[B]. \quad (7.3)$$

Assume that the control parameter ϵ in Eq. (7.1) is subjected to oscillatory perturbations $\epsilon = \epsilon_0 + \delta\epsilon(t)$. For a single frequency perturbation $\delta\epsilon(t) = \epsilon_1 \cos(\omega_1 t)$, the second-order nonlinear response will oscillate at frequencies $\pm 2\omega_1$, as shown in the Appendix. From Eqs. (A4) and (4.14b) we obtain a single-frequency quadratic signal

$$\chi^{(2)}(\omega_1, \omega_1) = -\frac{1}{4(f_x + \iota 2\omega_1)}$$
$$\times \left[\frac{f_{xx}f_\epsilon^2}{(f_x + \iota\omega_1)^2} + f_{\epsilon\epsilon} - \frac{2f_{x\epsilon}f_\epsilon}{f_x + \iota\omega_1}\right], \quad (7.4)$$

the f's are defined in the Appendix. This is plotted in Fig. 1(a) for the Schlögl model in Eqs. (7.2) and (7.3).

If the system is perturbed simultaneously at two frequencies, $\delta\epsilon(t) = \epsilon_1 \cos(\omega_1 t) + \epsilon_2 \cos(\omega_2 t)$, one can measure two-dimensional quadratic signal

$$\chi^{(2)}(\omega_1, \omega_2) = -\frac{1}{4(f_x + \iota(\omega_1 + \omega_2))}$$
$$\times \left[\frac{f_{xx}f_\epsilon^2}{(f_x + \iota\omega_1)(f_x + \iota\omega_2)} + f_{\epsilon\epsilon} - f_{x\epsilon}f_\epsilon\right.$$
$$\left.\times \left(\frac{1}{f_x + \iota\omega_1} + \frac{1}{f_x + \iota\omega_2}\right)\right], \qquad (7.5)$$
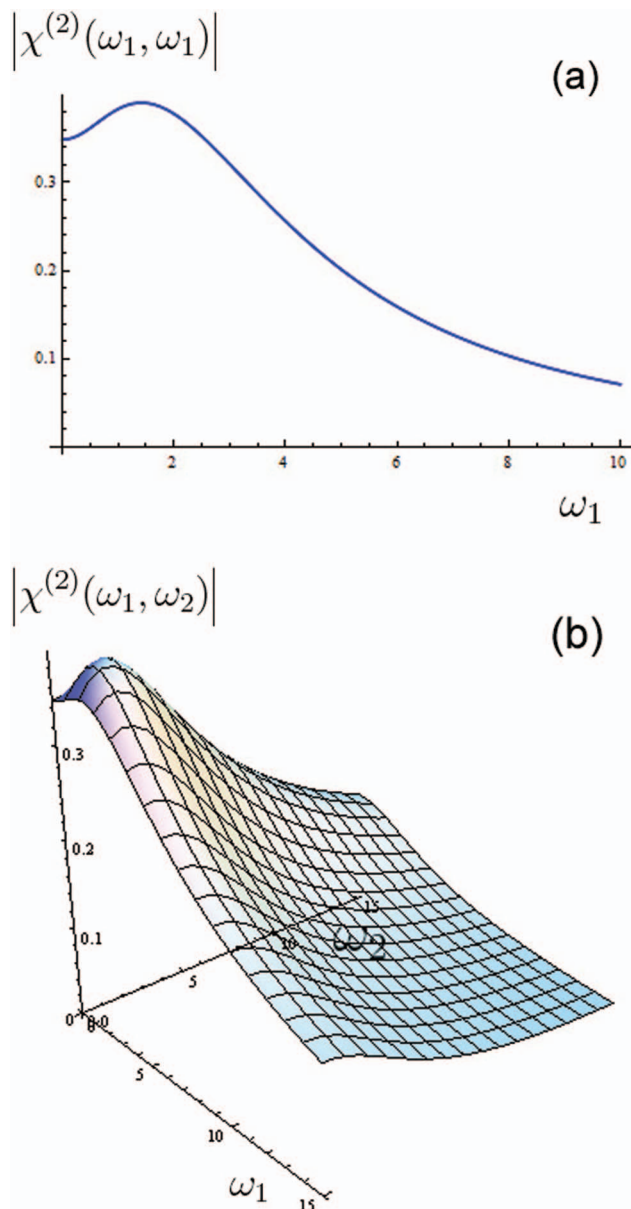
FIG. 1. Absolute value of the second order susceptibility for the Schlögl model in Eqs. (7.2) and (7.3): (a) single-frequency susceptibility $\chi^{(2)}(\omega_1, \omega_1)$, (b) two-frequencies susceptibility $\chi^{(2)}(\omega_1, \omega_2)$.

which follows from Eqs. (A5) and (4.15). The two-dimensional susceptibility $\chi^{(2)}(\omega_1, \omega_2)$ is plotted in Fig. 1(b) for the Schlögl model. Fig. 1(b) carries some additional information compared to Fig. 1(a). For instance, it is difficult to extract parameters such as $f_{\epsilon\epsilon}, f_{x\epsilon}, f_{xx}$ from Eq. (7.4) since it is rather complicated. However, they are much easier to extract from the two-dimensional signal $\chi^{(2)}(\omega_1, \omega_2)$: for large ω_1 Eq. (7.5) behaves as

$$\lim_{\omega_1 \to \infty} \mathrm{Im}\left[\omega_1 \chi^{(2)}(\omega_1, \omega_2)\right] = -\frac{1}{4}\left(f_{\epsilon\epsilon} - \frac{f_x f_{x\epsilon} f_\epsilon}{f_x^2 + \omega_2^2}\right).$$
(7.6)

It is straightforward to obtain the parameters $f_x, f_{\epsilon\epsilon}$, and $f_{x\epsilon} f_\epsilon$ of the Lorentzian in Eq. (7.6) by fitting. The product $f_{xx} f_\epsilon^2$
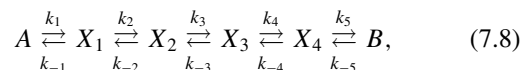
can be then determined from

$$\lim_{\omega_1 \to 0} \chi^{(2)}(\omega_1, \omega_1) = -\frac{1}{4f_x}\left(\frac{f_{xx} f_\epsilon^2}{f_x^2} + f_{\epsilon\epsilon} - \frac{2f_{x\epsilon} f_\epsilon}{f_x}\right).$$
(7.7)

Provided that f_ϵ is found from a linear experiment (see Eqs. (4.15), (A5a)) the two-dimensional second order susceptibility $\chi^{(2)}(\omega_1, \omega_2)$ allows to find all the second order derivatives $f_{\epsilon\epsilon}, f_{x\epsilon}, f_{xx}$, which characterize kinetic system in Eq. (7.1) at steady state. For the Schlögl model in Eq. (7.2) with $\epsilon \equiv [A]$ these parameters are $f_{xx} = -2k_2, f_{x\epsilon} = k_1$, and $f_{\epsilon\epsilon} = 0$. If information on system (7.1) beyond second order derivatives is needed, one can run higher order n-dimensional experiments involving $n + 1$ perturbations and measurements.

B. Multidimensional time domain signal

In Sec. VII A, we discussed a second order response experiment which consisted of two perturbations (one at frequency ω_1 and another at frequency ω_2) and a single measurement. Here, we discuss a different two-dimensional experiment which consists of one perturbation and two measurements. Such experiments can be used, for instance, to study the connectivity of complex reaction networks as demonstrated below.

Consider a chain of chemical reactions,

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} X_1 \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} X_2 \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} X_3 \underset{k_{-4}}{\overset{k_4}{\rightleftarrows}} X_4 \underset{k_{-5}}{\overset{k_5}{\rightleftarrows}} B,$$
(7.8)

in which the concentrations of species A and B are held constant by buffering, and each elementary reaction step can be either of linear (first order) or nonlinear (such as Michaelis-Menten) kinetics. Suppose that the reaction (7.8) is initially in steady state. We then impulsively perturb the concentration of species X_i at time t_1 and measure concentrations of species X_j and X_l at times t_2 and t_3, respectively. From this experiment, one can obtain a two-dimensional measure, as introduced in Sec. V,

$$R_{l+, j+, i-}(\tau_2, \tau_1) \equiv [X_i]_0^-(t_1)[X_j]_0(t_2)[X_l]_0(t_3)$$
(7.9)

that depends on two time intervals $\tau_1 = t_2 - t_1$ and $\tau_2 = t_3 - t_2$. In Eq. (7.9), we have used the conventional notation introduced in Ref. 30, in which "−" corresponds to perturbation and "+" to measurement.

In Fig. 2 we plot $R_{l+, j+, i-}(\tau_2, \tau_1)$ for the model in Eq. (7.8), in which all elementary steps are first-order reactions with $k_1 = \ldots = k_5 = 0.7$, $k_{-1} = k_{-3} = k_{-4} = 0.1$, $k_{-2} = 0.3$, $k_{-5} = 0.5$, $[A]_0 = 3$, $[B]_0 = 3$ and the chemical system is initially in steady state. From the two-dimensional plots in Fig. 2, one can make several observations. First, $[X_i]_0^-(t_1)[X_j]_0(t_2)[X_l]_0(t_3)$ has a long "memory" tail along the τ_2 axis in cases when species X_i in reaction network is closer to species X_j rather than to species X_l, i.e., the species are arranged in the order $X_i - X_j - X_l$. The latter can be
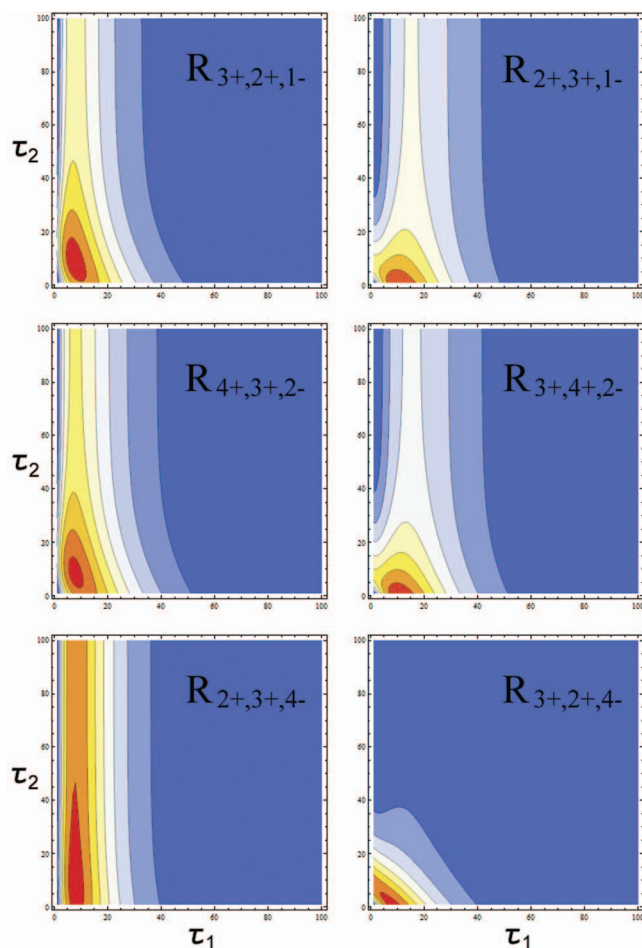
FIG. 2. Two-dimensional measures $R_{i+,j+,k-}(\tau_2, \tau_1) = [X_k]_0^-(0)[X_j]_0(\tau_1)$ $\times [X_i]_0(\tau_1 + \tau_2)$ for reaction chain in Eq. (7.8).

illustrated with the following example. If one considers a series of unidirectional first order reactions,

$$A_1 \xrightarrow{k} A_2 \xrightarrow{k} A_3 \xrightarrow{k} \ldots, \qquad (7.10)$$

in which only A_1 has non-zero initial concentration, then time behavior of concentrations $[A_i]$ are $[A_1] = [A_1](0)$ $\exp(-kt)$, $[A_2] = [A_1](0)kt \exp(-kt)$, $[A_3] = [A_1](0)k^2t^2$ $\exp(-kt)/2$, and so on. The maximum of $[A_2]$ is achieved at $t_{2,\max} = 1/k$, while the maximum of $[A_3]$ is achieved at $t_{3,\max} = \sqrt{2}/k$, i.e., signal propagates in reaction network from left to right. From the latter time behavior of concentrations it follows that the product $[A_2](\tau_1)[A_3](\tau_1 + \tau_2)$ at large times τ_2 behaves as $\sim \tau_2^2 \exp(-k\tau_2)$ and thus is more stretched along τ_2 than the product $[A_3](\tau_1)[A_2](\tau_1 + \tau_2)$ which behaves as $\sim \tau_2 \exp(-k\tau_2)$. For the same reason, the 2D plots $[X_1]_0^-(0)[X_2]_0(\tau_1)[X_3]_0(\tau_1 + \tau_2)$, $[X_2]_0^-(0)[X_3]_0(\tau_1)[X_4]_0(\tau_1 + \tau_2)$, and $[X_4]_0^-(0)[X_3]_0(\tau_1)$ $[X_2]_0(\tau_1 + \tau_2)$ in Fig. 2 have longer tails along the τ_2 axis, than the plots $[X_1]_0^-(0)[X_3]_0(\tau_1)[X_2]_0(\tau_1 + \tau_2)$, $[X_2]_0^-(0)[X_4]_0(\tau_1)[X_3]_0(\tau_1 + \tau_2)$, and $[X_4]_0^-(0)[X_2]_0(\tau_1)$ $[X_3]_0(\tau_1 + \tau_2)$. The latter observations allow one to restore the arrangement of species X_i in the reaction network, which is found to be

$$X_1 - X_2 - X_3 - X_4. \qquad (7.11)$$
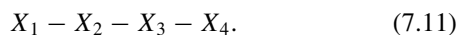
Another observation that can be made from Fig. 2 is that 2D plots corresponding to correct ordering of species in the reaction chain (left column in Fig. 2) show a well-defined peak at (τ_1^0, τ_2^0). It is yet another illustration of the perturbation propagation mechanism described in the previous paragraph. If the maximum change in concentration of X_j (X_l) is achieved at time τ_1^0 ($\tau_1^0 + \tau_2^0$) after a perturbation of X_i, then the correlation function $\langle [X_j](\tau_1)[X_l](\tau_1 + \tau_2) \rangle$ will have its maximum value at $(\tau_1, \tau_2) = (\tau_1^0, \tau_2^0)$. For the same reason the correlation function $\langle [X_l](\tau_1)[X_j](\tau_1 + \tau_2) \rangle$ does not have a peak, since $[X_l](\tau_1)$ and $[X_j](\tau_1 + \tau_2)$ cannot simultaneously reach their maximum values for any $\tau_1 > 0$ and $\tau_2 > 0$.

One should note that the multidimensional picture provided by the measure $R_{l+,j+,i-}(\tau_2, \tau_1)$ allows easier conclusions on the above observations such as longer memory tails for correct order of species and peak position corresponding to delay in signal propagation. The latter conclusions would be less obvious from one-dimensional techniques.

VIII. DISCUSSION

We have developed a theory of nonlinear response in chemical kinetics. By subjecting a chemical system to n perturbations one can measure the nth order nonlinear response function, which depends on n time intervals between perturbations and a measurement and thus acts as an n-dimensional characteristics of the chemical system of interest. Multidimensional characteristics such as nonlinear response functions contain significantly more detailed information on chemical dynamics and mechanisms of chemical reactions than one-dimensional techniques.

In Sec. V, we extended the concept of nonlinear response, and introduced a different class of experiments that employ a combination of multiple perturbations and multiple measurements. These generalized experiments produce a new class of multidimensional measures called generalized response functions, which can carry complementary information to the ordinary nonlinear response functions. Although some generalized and ordinary response functions may be related via fluctuation-dissipation expressions, they can serve as alternative or more convenient tools to collect or represent multidimensional information about the chemical system. Fluctuation-dissipation relations also provide a way to substitute measurements of unaccessible concentrations of particular species with rather straightforward perturbations of their concentrations.

We have provided formal closed expressions of multidimensional measures that can be obtained from chemical experiments with multiple perturbations and measurements. These expressions depend on stability derivatives which carry additional information about the underlying chemical dynamics. Coupled with further analyses and applications of multidimensional techniques to complex chemical systems, the derived multidimensional measures will help better understand information contained in the measured signals. In Sec. VII, we gave two such examples and showed that multidimensional techniques can be useful tools to reveal the mechanism of chemical reactions.

ACKNOWLEDGMENTS

APPENDIX: SECOND-ORDER RESPONSE OF A NONLINEAR ONE-VARIABLE KINETIC SCHEME

In this Appendix, we derive expressions for second-order response of the single-variable kinetic scheme in Eq. (7.1). One can expand solution of the perturbed Eq. (7.1) as

$$x(t) = x_0 + x^{(1)}(t) + x^{(2)}(t) + \dots, \tag{A1}$$

where $x^{(n)}$ is on the order of ϵ_1^n and x_0 is a steady-state solution of the unperturbed system. Expanding $f(x, \epsilon)$ around x_0, ϵ_0 and

collecting terms of the same order, one gets

$$\frac{dx^{(1)}}{dt} = f_x x^{(1)} + f_\epsilon \delta\epsilon,$$

$$\frac{dx^{(2)}}{dt} = f_x x^{(2)} + \frac{1}{2} f_{xx} (x^{(1)})^2 + \frac{1}{2} f_{\epsilon\epsilon} (\delta\epsilon)^2 + f_{x\epsilon} x^{(1)} \delta\epsilon, \tag{A2}$$

where $f_x = \partial f(x_0)/\partial x$. Taking the Fourier transform $\mathcal{F}[f] = \int dt\, f(t) \exp(\iota\omega t) = \widetilde{f}(\omega)$ of Eq. (A2), one gets

$$\widetilde{x}^{(1)}(\omega) = -\frac{f_\epsilon}{f_x + \iota\omega} \widetilde{\delta\epsilon}(\omega)$$

$$\widetilde{x}^{(2)}(\omega) = -\frac{1}{f_x + \iota\omega} \left(\frac{1}{2} f_{xx} \mathcal{F}[(x^{(1)})^2] + \frac{1}{2} f_{\epsilon\epsilon} \mathcal{F}[(\delta\epsilon)^2] + f_{x\epsilon} \mathcal{F}[x^{(1)} \delta\epsilon] \right). \tag{A3}$$

In case of single-frequency perturbation, $\delta\epsilon = \epsilon_1 \cos(\omega_1 t)$, which has been also discussed in Ref. 14, Eqs. (A3) result in the following:

$$\widetilde{x}^{(1)}(\omega) = -\frac{f_\epsilon \epsilon_1}{f_x + \iota\omega} \pi \left(\delta(\omega - \omega_1) + \delta(\omega + \omega_1) \right),$$

$$\widetilde{x}^{(2)}(\omega) = -\frac{\epsilon_1^2}{f_x + \iota\omega} \pi \left\{ \delta(\omega - 2\omega_1) \left[\frac{f_{xx} f_\epsilon^2}{4(f_x + \iota\omega_1)^2} + \frac{f_{\epsilon\epsilon}}{4} - \frac{f_{x\epsilon} f_\epsilon}{2(f_x + \iota\omega_1)} \right] \right. \tag{A4}$$

$$+ \delta(\omega + 2\omega_1) \left[\frac{f_{xx} f_\epsilon^2}{4(f_x - \iota\omega_1)^2} + \frac{f_{\epsilon\epsilon}}{4} - \frac{f_{x\epsilon} f_\epsilon}{2(f_x - \iota\omega_1)} \right]$$

$$+ \left. \delta(\omega) \left[\frac{f_{xx} f_\epsilon^2 - 2 f_{x\epsilon} f_\epsilon f_x}{2\left(f_x^2 + \omega_1^2\right)} + \frac{f_{\epsilon\epsilon}}{2} \right] \right\}.$$

We note that if perturbation in Eq. (7.1) can be expressed in the form of Eq. (4.8), i.e., when $f_{\epsilon\epsilon} = 0$, then Eqs. (A4) could also be obtained from Eq. (4.12) by evaluating action of the differential operators $\widetilde{\mathcal{D}}_0(\omega) = \mathcal{F}[\mathcal{D}_0(t)] = \mathcal{F}[\exp(t f(x)\partial/\partial x)] = 1/[\iota\omega + (f_x(x - x_0) + f_{xx}(x - x_0)^2/2)\partial/\partial x]$ and $V_- = (f_\epsilon + f_{x\epsilon}(x - x_0))\partial/\partial x$ at $x = x_0$.

In case of perturbation on two frequencies, $\delta\epsilon = \epsilon_1 \cos(\omega_1 t) + \epsilon_2 \cos(\omega_2 t)$, Eqs. (A3) result in the following:

$$\widetilde{x}^{(1)}(\omega) = -\frac{f_\epsilon}{f_x + \iota\omega} \pi \left[\epsilon_1 \left(\delta(\omega - \omega_1) + \delta(\omega + \omega_1) \right) + \epsilon_2 \left(\delta(\omega - \omega_2) + \delta(\omega + \omega_2) \right) \right], \tag{A5a}$$

$$\widetilde{x}^{(2)}(\omega) = -\frac{\epsilon_1 \epsilon_2}{f_x + \iota\omega} \pi \left\{ \delta(\omega - \omega_1 - \omega_2) \left[\frac{f_{xx} f_\epsilon^2}{4(f_x + \iota\omega_1)(f_x + \iota\omega_2)} \right. \right.$$

$$+ \left. \frac{f_{\epsilon\epsilon}}{4} - \frac{f_{x\epsilon} f_\epsilon}{4} \left(\frac{1}{f_x + \iota\omega_1} + \frac{1}{f_x + \iota\omega_2} \right) \right]$$

$$+ \delta(\omega + \omega_1 + \omega_2) \left[\frac{f_{xx} f_\epsilon^2}{4(f_x - \iota\omega_1)(f_x - \iota\omega_2)} \right.$$

$$+ \left. \left. \frac{f_{\epsilon\epsilon}}{4} - \frac{f_{x\epsilon} f_\epsilon}{4} \left(\frac{1}{f_x - \iota\omega_1} + \frac{1}{f_x - \iota\omega_2} \right) \right] + \dots \right\}, \tag{A5b}$$

where in the last equation we explicitly wrote only expressions for the two peaks at $\omega = \pm(\omega_1 + \omega_2)$.

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