

## Normal Modes for Chemical Reactions from Time Series Analysis

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A method is presented for probing chemical reaction mechanisms experimentally with perturbations and measurements of the response. Time series analysis and the methods of linear control theory are used to determine the Jacobian matrix of a reaction at a stable stationary state subjected to random perturbations. The method is demonstrated with time series of a model system, and its performance in the presence of noise is examined.

### I. Introduction

The dynamical behavior of a chemical reaction close to a stationary state is described by the elements of the associated Jacobian matrix. If a fully specified model is known for a system, it is straightforward to calculate the stationary state and the corresponding Jacobian matrix. However, the reverse problem of deducing the mechanism from a knowledge of the Jacobian is much more difficult, and, in addition, such problems do not afford unique solutions. Nevertheless, valuable information about the mechanism can be gleaned from a knowledge of the Jacobian matrix.<sup>1</sup> In fact, mechanistic insights can be obtained even if only a part of the matrix or just the signs of the elements are known.<sup>2–6</sup> Most of the methods that have been proposed for experimental determination of the Jacobian require the ability to measure the concentrations of all species that significantly affect the dynamics. Unfortunately, this condition is often not met in practice.

A previously developed method, called quenching analysis,<sup>7</sup> overcomes many of these difficulties by carrying out the chemical reaction in a continuous-flow stirred tank reactor (CSTR) close to a supercritical Hopf bifurcation. The operating conditions are adjusted such that the system shows small-amplitude sinusoidal limit cycle oscillations around a saddle focus. For each of the essential species there exists a characteristic perturbation magnitude and phase of the oscillation for which the oscillatory behavior can be temporarily stopped (quenched) by the effectively instantaneous addition of an appropriate compound. The perturbation moves the current state of the system from the limit cycle to the codimension-two stable manifold of the saddle focus, from which it slowly returns to the limit cycle. This behavior is universal for a chemical system near a supercritical Hopf bifurcation. Observing the concentration of just one of the essential species and measuring the quenching parameters for  $n$  essential species allows the calculation of the  $2n$  elements of the two left eigenvectors associated with the Hopf oscillatory mode. The corresponding right eigenvectors of the Jacobian matrix can be determined by additional measurements of the oscillating concentrations of  $n - 3$  of the remaining species.<sup>8</sup> The concentrations of the

stationary state can then be computed from an additional quenching experiment performed by an instantaneous dilution of the system. The quenching method has been used to investigate the mechanisms of a number of different chemical systems.<sup>9,10</sup>

In this paper we present a new method for determining the complete Jacobian matrix of an  $n$ -species chemical system in a stable stationary state. The method consists of making  $n$  time series measurements of a single property that is a linear (but not necessarily known) function of the concentrations. In each series of measurements, a different set of species is subjected to random known perturbations at regular time intervals. If some of the characteristic times are much smaller than the time interval of the measurements, it is then not possible to determine the complete Jacobian; however, the method allows the computation of the characteristic times of the remaining slow modes together with the corresponding left eigenvectors of the Jacobian matrix.

### II. Method

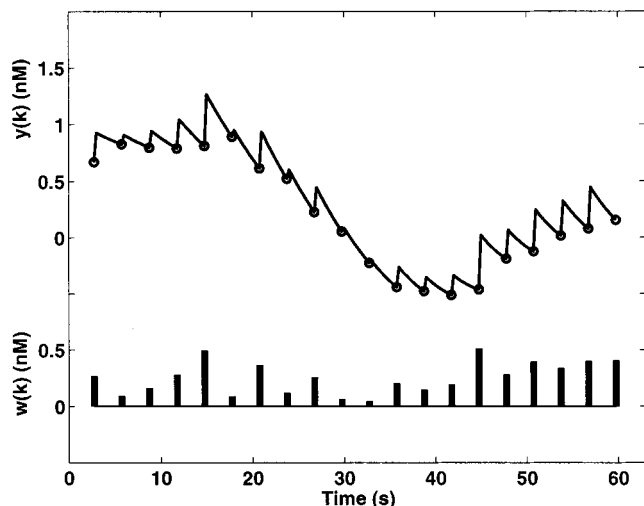
Following linear control theory,<sup>11</sup> we write an autoregression equation for successive measurements and perturbations of a chemical system very close to a stable stationary state.<sup>12</sup> The measured quantity is typically some linear function of the concentrations of the dynamical species, such as optical absorbance. Considering an  $n$ -dimensional chemical system that is perturbed at equal time intervals by the addition of one (or more) of the dynamically important species, the autoregression equation takes the form

$$y_k = a_1 y_{k-1} + a_2 y_{k-2} + \dots + a_n y_{k-n} + b_0 + b_1 w_{k-1} + b_2 w_{k-2} + \dots + b_n w_{k-n} \quad (1)$$

where  $y_k$  is the measured quantity and  $w_k$  is the magnitude of the perturbation at time  $t_k$ . This equation is often seen without the bias term,  $b_0$ , which can always be set to zero by a suitable scaling for the  $y$  measurements. We find it convenient, however, to consider  $b_0$  as a parameter that is identified from the experimental data in the same step as the other coefficients  $a_i$  and  $b_i$ . It is necessary to carry out at least  $3n + 1$  readings of  $y$  in order to obtain the  $2n + 1$  equations needed to determine the  $2n + 1$  coefficients. However, in practice, many more

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**Figure 1.** Perturbations  $w_k$  and time series of responding chemical system  $y_k = (Z - Z_s)$ . Calculations were carried out using the three-variable Oregonator model, identical to model M3 described in Nielsen et al.<sup>17</sup> The system is perturbed by making momentary changes in the variable  $Z = [\text{Ce}^{4+}]$ . The perturbations are random in magnitude, drawn from a uniform distribution in the interval from 0.0 to 0.5 nM. The measurements of  $Z$  are made at 3.0 s intervals (indicated by circles), and a perturbation is made immediately after each measurement. All parameters are the same as in Nielsen et al.<sup>17</sup> except  $[\text{H}^+]$  is changed from 1.0 to 0.8 M to produce a weakly stable system. The stationary state concentrations for the three variable species are  $X_s = 2.84 \times 10^{-8}$  M,  $Y_s = 2.17 \times 10^{-7}$  M, and  $Z_s = 1.37 \times 10^{-7}$  M.

readings are typically required to adequately determine the coefficients, due to unavoidable noise. The method of singular value decomposition (SVD)<sup>13,14</sup> allows the coefficients to be accurately estimated from the overdetermined system. The magnitudes of the perturbations,  $w_k$ , are randomly varied in order to ensure that the equations determining the coefficients  $a_i$  and  $b_i$  can be solved. Alternatively, perturbations with the same magnitude can be made at irregular intervals.

In Figure 1, we show a specific example of the identification procedure. We use time series generated by integrating the Oregonator model<sup>15</sup> of the Belousov–Zhabotinsky<sup>16</sup> (BZ) reaction, with parameters adjusted to fit results from previous quenching experiments.<sup>17,18</sup> The model parameters were chosen so that the chemical system exhibits a stable stationary state. The Oregonator model includes three essential chemical species,  $\text{HBrO}_2$ ,  $\text{Br}^-$ , and  $\text{Ce}^{4+}$ , designated  $X$ ,  $Y$ , and  $Z$ , with concentrations  $X$ ,  $Y$ , and  $Z$ . The eigenvalues of the Jacobian at the stationary point are  $-0.34$  and  $-0.012 \pm i0.087$ . The upper curve shows the evolution of the concentration  $Z$  in response to the perturbations shown in the lower part of the figure. The circles indicate the sampling points. The coefficients of the autoregression eq 1 for the three-dimensional model were determined from 500 readings of  $Z$  and the corresponding random perturbations at 3.0 s intervals. The singular value decomposition yields the following values:<sup>19</sup>

$$(a_1, a_2, a_3) = (2.215, -1.586, 0.338)$$

$$(b_1, b_2, b_3) = (0.589, -1.031, 0.328)$$

In simulations, the adequacy of the coefficients obtained from the autoregression model can be readily checked by comparing the predicted signal with the original computed signal. The residual error is quite small, with the one-step prediction of  $Z$  by the autoregression model virtually indistinguishable from the time series shown in Figure 1.

The numerical experiment was carried out three times, with perturbations applied, in turn, to the  $X$ ,  $Y$ , and  $Z$  concentration variables of the model. The measured variable in each case was  $Z$ . The range of perturbation magnitudes for each run was chosen to yield responses of similar magnitude in  $Z$ . For the perturbations in  $X$ ,  $Y$ , and  $Z$ , the maximum magnitudes were  $1.7 \times 10^{-10}$ ,  $3.9 \times 10^{-10}$ , and  $5.2 \times 10^{-10}$  M, respectively. The coefficients of the associated autoregression models were then used to determine the elements of the Jacobian matrix as described below.

### III. Computing the Jacobian Matrix

In a series of measurements and perturbations, the perturbation at time  $t_k$  results in a shift  $w_k \mathbf{g}$  in concentration space in a fixed direction given by the vector  $\mathbf{g}$ . The coefficients  $a_j$  and  $b_j$  of the autoregression equation (1) for the series can now be used to write the following matrices:

$$\mathbf{L} = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ a_3 & a_2 & a_1 \end{pmatrix}$$

$$\mathbf{C} = \begin{pmatrix} 1 & 0 & 0 \\ -a_1 & 1 & 0 \\ -a_2 & -a_1 & 1 \end{pmatrix}$$

$$\mathbf{b} = \begin{pmatrix} b_1 \\ b_2 \\ b_3 \end{pmatrix}$$

The coefficients  $a_j$  are characteristic of the dynamics of the unperturbed system and are independent of the direction of perturbation, whereas the coefficients  $b_j$  depend on  $\mathbf{g}$ . By carrying out three different series with perturbations in three directions, given by the linearly independent vectors,  $\mathbf{g}_1$ ,  $\mathbf{g}_2$ , and  $\mathbf{g}_3$ , we obtain three different vectors,  $\mathbf{b}_1$ ,  $\mathbf{b}_2$ , and  $\mathbf{b}_3$ . These vectors can be combined in matrices  $\mathbf{G} = (\mathbf{g}_1, \mathbf{g}_2, \mathbf{g}_3)$  and  $\mathbf{B} = (\mathbf{b}_1, \mathbf{b}_2, \mathbf{b}_3)$ , with the vectors  $\mathbf{g}$  and  $\mathbf{b}$  as columns. Using  $\mathbf{G}$  and  $\mathbf{B}$ , we can now compute the matrix  $\mathbf{F}$  governing the discrete dynamics corresponding to a fixed sampling interval  $\Delta t$ ,

$$\mathbf{F} = \mathbf{GB}^{-1}\mathbf{CLC}^{-1}\mathbf{BG}^{-1} \quad (2)$$

and hence the Jacobian matrix from the relation

$$\mathbf{F} = e^{\mathbf{J}\Delta t} \quad (3)$$

The development of eqs 2 and 3 can be found in the Appendix.

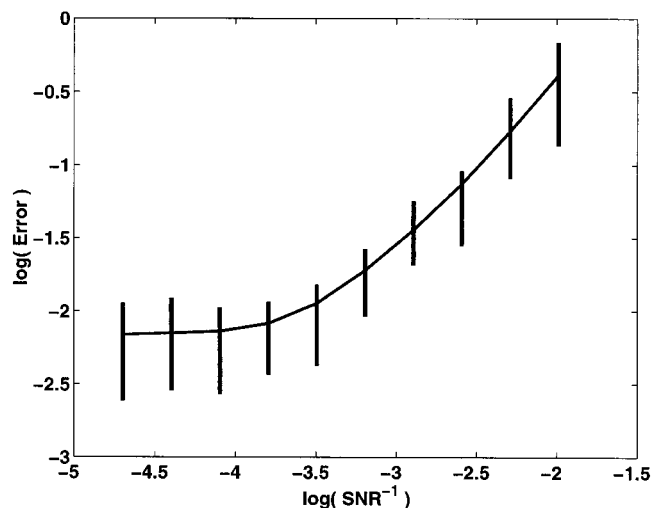
### IV. Results

Repeating the integration of the Oregonator model, first with  $\text{Br}^-$  ( $Y$ ) and then with  $\text{HBrO}_2$  ( $X$ ) replacing  $\text{Ce}^{4+}$  ( $Z$ ) as the perturbed species, we obtain the same  $a$  coefficients but different  $b$  coefficients. This procedure makes  $\mathbf{G}$  equal to the 3D identity matrix, since in each case the perturbation vector,  $\mathbf{g}$ , is directed along one of the coordinate axes in concentration space.

Forming the matrices  $\mathbf{L}$ ,  $\mathbf{C}$ ,  $\mathbf{B}$ , and  $\mathbf{G}$  and inserting them into eqs 2 and 3 results in the following Jacobian matrix (in units of  $\text{s}^{-1}$ ):

$$\mathbf{J} = \begin{pmatrix} -0.121 & -0.052 & 0.000 \\ -0.530 & -0.084 & 0.131 \\ 0.811 & 0.000 & -0.165 \end{pmatrix}$$

in good agreement with the Jacobian matrix calculated directly



**Figure 2.** Dependence of the relative Jacobian error on the signal to noise ratio. Uniform noise is added to the measurements of  $y_k$  and the relative Jacobian error is shown as a function of relative noise amplitude. The vertical lines show the standard deviation from the mean values for 40 numerical experiments. The abscissa is the logarithm of the rms of the noise relative to the rms of the signal. The relative Jacobian error is defined as the Euclidian norm of the difference between the analytical and reconstructed Jacobians divided by the Euclidian norm of the analytical Jacobian, where the Euclidian norm is the square root of the sum of the squared elements. Parameters and procedures are the same as in Figure 1.

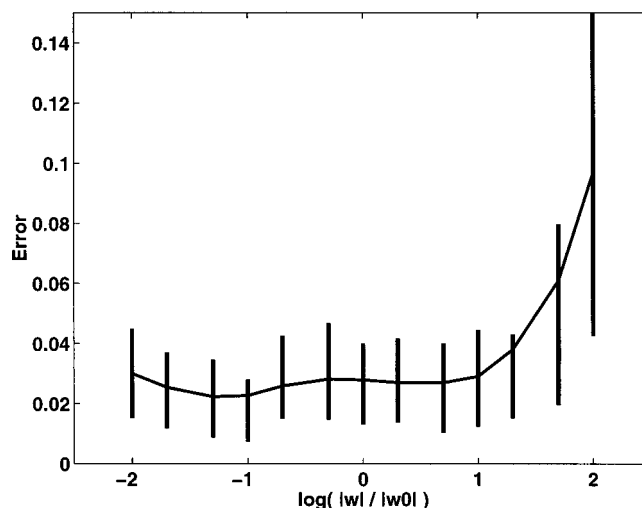
from the Oregonator model:

$$\mathbf{J} = \begin{pmatrix} -0.1174 & -0.0528 & 0.0000 \\ -0.5202 & -0.0835 & 0.1320 \\ 0.8064 & 0.0000 & -0.1670 \end{pmatrix}$$

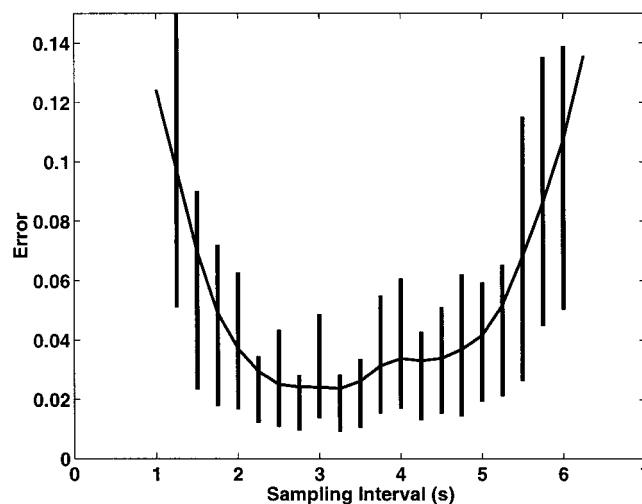
In an actual experiment, the signal to noise ratio (SNR) is limited due to uncontrollable external fluctuations. It is therefore important to assess the robustness of the method in the presence of noise. Figure 2 shows the relative Jacobian error as a function of the SNR. We see that the error increases proportionally with the noise level above a certain level. It is important to note that the effect of noise on the reconstructed Jacobian error depends sensitively on the eigenvalues and a degradation of performance occurs even at low noise levels in very stiff systems. A small amount of noise (0.1% of the signal amplitude) was added to the measured variable in each of the following calculations in order to simulate realistic experimental measurements.

The Jacobian error reflects noise in the data and nonlinearities of the system, which can, to some extent, be separated by varying the amplitude of the perturbations. Excessively large perturbations result in deviations from the linear regime and degrade the precision of the reconstructed Jacobian. Perturbations that are too small, on the other hand, reduce the available signal to noise ratio and are also undesirable. These trends can be seen in Figure 3, which shows the relative Jacobian error as a function of perturbation amplitude. We see that the perturbation amplitude can be as large as  $5.2 \times 10^{-9}$  M, which is about 4.0% of the stationary state concentration ( $Z_s = 1.37 \times 10^{-7}$  M), before the relative Jacobian error begins to increase. Perturbation amplitudes of about 1.0% of the stationary state concentration give rise to a relative Jacobian error of about 3.0%.

There is similarly an optimal choice of the sampling interval, as shown in Figure 4. The faster dynamical modes become unobservable for very long sampling intervals, while very short sampling intervals give rise to measured signals primarily reflecting the noise. The optimal value of the sampling interval

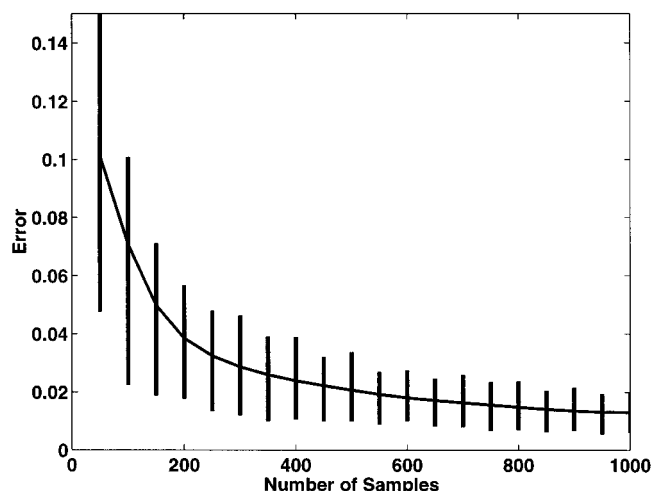


**Figure 3.** Dependence of the relative Jacobian error on the perturbation amplitude. The solid curve shows the error as a function of the maximum perturbation  $\|w\|$  relative to  $\|w_0\| = 0.5$  nM as in Figure 1. The perturbation amplitudes for  $X$  and  $Y$  were also varied proportionally, as each Jacobian reconstruction requires data from three experiments, with each interrogating one of the variables. The vertical lines show the standard deviation from the mean values for 40 numerical experiments. Low-level noise (0.1% of the signal amplitude) was added to the measured variable. The parameters and procedures are the same as those for Figure 1. The relative Jacobian error is defined in Figure 2.



**Figure 4.** Dependence of the relative Jacobian error on the sampling interval. The solid curve shows the error as a function of the sampling interval, and the vertical lines show the standard deviation from the mean values for 40 numerical experiments. Low-level noise (0.1% of the signal amplitude) was added to the measured variable. Parameters and procedures are the same as in Figure 1, except that the perturbation amplitude was adjusted to maintain a constant amplitude of the response signal. The relative Jacobian error is defined in Figure 2.

is therefore a complex function of the system time scales and properties of the noise. The variation in the coefficients during a particular experiment or from experiment to experiment can serve as an empirical measure of the robustness of the autoregression model. We see in Figure 4 that a 3.0 s sampling interval is close to the optimal value, which is comparable to the reciprocal eigenvalues of  $\mathbf{J}$ . It should also be noted that a large variation in the Jacobian error was observed between individual runs. It is frequently possible to obtain errors as low as 1.0% with an optimal choice of parameters, but large errors occasionally occur, which limits the average precision to approximately 3.0%.



**Figure 5.** Dependence of the relative Jacobian error on the number of samples. The solid curve shows the error as a function of the total number of samples used with each dynamical variable in reconstructing the Jacobian. The vertical lines show the standard deviation from the mean values for 40 numerical experiments. Low-level noise (0.1% of the signal amplitude) was added to the measured variable. Parameters and procedures are the same as in Figure 1. The relative Jacobian error is defined in Figure 2.

Reconstruction of the Jacobian depends upon the precision of the autoregression model obtained from the experimental data. Increasing the number of samples results in a more precise autoregression model. Using the same parameters as above, we show in Figure 5 the relative Jacobian error as a function of the number of data pairs collected in each numerical experiment (for each dynamical variable). We see in this particular example that there is no significant advantage in increasing the number of samples above approximately 500 data pairs. We have not determined how this error dependence varies with different dynamical systems.

We note that the identification procedure can be carried out in an alternative manner that may be advantageous in actual experiments. Rather than random amplitude perturbations delivered at constant time intervals, constant amplitude perturbations can be delivered at nonperiodic time intervals. Identical values for the coefficients ( $a_1, a_2, a_3$ ) and ( $b_1, b_2, b_3$ ) were obtained when the calculation for Figure 1 was repeated using perturbations at time intervals that were  $t_i/(3.0 \text{ s})$  multiples of 7, 13, or 17. This scheme has the advantage that constant perturbations can be delivered more accurately and conveniently in an experimental setting. In addition, fewer perturbations are required for the system identification, and the system state is therefore moved away from the stationary state less than it would be with constant time interval perturbations.

## V. Discussion

The determination of chemical reaction mechanisms is often difficult, particularly for complex reactions, because no systematic methods exist for identifying the essential component steps of a reaction. Chemical mechanisms are usually deduced by considering combinations of elementary steps that give rise to a scheme consistent with the experimentally measured chemical kinetics of the reaction. Relaxation kinetics offers a convenient approach for experimentally probing chemical mechanisms. Originally developed by Eigen and co-workers,<sup>20</sup> the technique involves monitoring relaxations very close to the equilibrium state such that the reaction follows first-order kinetics. Relaxation methods have been utilized extensively for

the investigation of chemical mechanisms, particularly for very fast reactions.<sup>21</sup> Recently, there has been renewed interest in perturbation methods for mechanism elucidation, in which the dynamical behavior around a nonequilibrium stationary state is probed. Quenching techniques, where an oscillatory reaction is driven to its unstable stationary state by precisely timed perturbations, have been successfully applied to several experimental chemical systems.<sup>7–10</sup> These studies have focused on the Jacobian matrix of the nonequilibrium stationary state to provide insights into the possible restrictions of a scheme of mechanistic steps. The elements of the Jacobian matrix tell how each dynamical species responds to all of the other dynamical species, as well as to itself, and therefore provide vital information on allowed and forbidden steps in a chemical mechanism.<sup>1</sup>

Determining the Jacobian matrix from experimental data and deducing a reaction mechanism that is consistent with the Jacobian elements is an important challenge. A number of studies have recently considered this problem in efforts to develop a systematic approach for mechanism elucidation.<sup>2–6</sup> In this paper, we have addressed the essential step of determining the Jacobian matrix from experimental data. Our approach is based on classical linear control theory, where a system in a stationary or periodic state is subjected to very small, random perturbations to determine the “normal modes” of the reaction. The perturbations and corresponding responses form a discrete time series as a sequence of data pairs that can be analyzed to yield the Jacobian matrix.

In principle, the Jacobian can be unambiguously determined from time series analysis of a chemical reaction subjected to random perturbations, provided that the system is observable and controllable.<sup>22</sup> In practice, however, there are uncertainties that pose technical challenges to the method. The first is ascertaining all of the dynamically important species and then devising a means to impose perturbations on each of these species. As we have noted, the method yields useful mechanistic information even if some of the essential species cannot be accessed. The other limitation is the effect of noise on the accuracy of the Jacobian matrix elements when applying the method in an experimental setting. For some systems, the method is quite robust to external noise; however, for other systems, especially those with a large negative eigenvalue, noise may significantly degrade the reliability of the Jacobian matrix. It should still be possible in such cases to determine the sign of the Jacobian matrix elements, which can offer valuable insights into the mechanistic possibilities of a chemical reaction. There are other well-known controllability and observability pathologies, such as degenerate eigenvalues, that cause the method to fail.<sup>22</sup> On the other hand, in favorable cases the method can offer an experimental means to determine the possible chemical steps as well as the associated rate constants.

We have shown that the Jacobian matrix of a chemical system in a stable stationary state can be determined from the time series of a single observable variable by applying perturbations to the relevant chemical species. If some of the modes of the system are too fast to be measured by the method, the information on the remaining modes can still be recovered. The performance of the method depends upon an appropriate choice of the perturbation magnitude and sampling interval, and, in general, increases with an increasing amount of data available for processing. The method can be readily applied to higher-dimensional chemical systems by a straightforward extension of the corresponding vectors and matrices.

## Appendix

The kinetic equations for a homogeneous chemical system with  $n$  chemical species can be written as

$$d\mathbf{c}(t)/dt = \mathbf{f}(\mathbf{c}(t)) \quad (4)$$

where the column vector  $\mathbf{c}(t)$  describes the time-dependent concentrations. We assume that the system has a stationary state,  $\mathbf{c}_s$ . A linear expansion of the kinetic equations around the stationary state gives

$$d\mathbf{u}(t)/dt = \mathbf{J} \cdot \mathbf{u}(t) + \dots \quad (5)$$

where  $\mathbf{u}(t) = \mathbf{c}(t) - \mathbf{c}_s$  describes the deviation from the stationary state and  $\mathbf{J}$  is the Jacobian matrix with elements  $J_{ij} = (\partial f_i(\mathbf{c}) / \partial c_j)|_{\mathbf{c}=\mathbf{c}_s}$ . We consider values of  $\mathbf{u}(t)$  at a set of equidistant discrete moments  $t_k$ . The vectors  $\mathbf{u}(t_k)$  and  $\mathbf{u}(t_{k-1})$  are formally related by the expression

$$\mathbf{u}(t_k) = e^{\mathbf{J}\Delta t} \mathbf{u}(t_{k-1}) \quad (6)$$

where  $\Delta t = t_k - t_{k-1}$ . The matrix  $\mathbf{F} = e^{\mathbf{J}\Delta t}$  has the same eigenvectors as  $\mathbf{J}$  and has eigenvalues  $\rho_j = e^{\lambda_j \Delta t}$ , where  $\lambda_j$  are the eigenvalues of  $\mathbf{J}$ .

The evolution of the chemical system is monitored by measuring a property  $y(t)$ , which is a function of  $\mathbf{c}(t)$ . A linear expansion of  $y$  from  $y_s = y(\mathbf{c}_s)$  gives

$$z = y - y_s = \mathbf{h}^T \cdot \mathbf{u} \quad (7)$$

where  $\mathbf{h}$  is the vector of coefficients of the first-order terms in the expansion. All essential changes in the system are reflected in  $y(t)$ , provided that the matrix

$$\mathbf{A} = \begin{pmatrix} \mathbf{h}^T \\ \mathbf{h}^T \cdot \mathbf{F} \\ \mathbf{h}^T \cdot \mathbf{F}^2 \\ \vdots \\ \mathbf{h}^T \cdot \mathbf{F}^{n-1} \end{pmatrix} \quad (8)$$

is of rank  $n$  (the observability condition).<sup>22</sup>

We follow Lee<sup>22</sup> in the subsequent transformations leading to the identification of the Jacobian matrix elements. Perturbations are applied to the system at  $t_k$  resulting in an instantaneous concentration change of  $\mathbf{g}w_k$ . To ensure that the perturbation excites all of the characteristic modes, the vector  $\mathbf{g}$  must be selected such that the matrix

$$(\mathbf{g}, \mathbf{F} \cdot \mathbf{g}, \mathbf{F}^2 \cdot \mathbf{g}, \dots, \mathbf{F}^{n-1} \cdot \mathbf{g}) \quad (9)$$

has rank  $n$  (the controllability condition).<sup>22</sup> By convention, the perturbation at any time  $t_k$  is made immediately after the measurement and therefore does not affect the value measured at  $t_k$ . Successive  $\mathbf{u}_k$  and  $z_k = z(t_k)$  are related by

$$\begin{aligned} \mathbf{u}_k &= \mathbf{F} \cdot (\mathbf{u}_{k-1} + \mathbf{g}w_{k-1}) \\ &= \mathbf{F} \cdot \mathbf{u}_{k-1} + \mathbf{F} \cdot \mathbf{g}w_{k-1} \end{aligned} \quad (10)$$

$$z_k = \mathbf{h}^T \cdot \mathbf{u}_k$$

By direct substitution it can be shown that the coordinate

transformation  $\mathbf{v} = \mathbf{A} \cdot \mathbf{u}$  transforms eq 10 into the canonical form

$$\mathbf{v}_k = \mathbf{L} \cdot \mathbf{v}_{k-1} + \mathbf{d}w_{k-1} \quad (11)$$

$$z_k = (1, 0, \dots, 0) \cdot \mathbf{v}_k$$

where

$$\mathbf{L} = \mathbf{A} \cdot \mathbf{F} \cdot \mathbf{A}^{-1} = \begin{pmatrix} 0 & 1 & 0 & \dots & 0 \\ 0 & 0 & 1 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & 1 \\ L_{n1} & L_{n2} & L_{n3} & \dots & L_{nn} \end{pmatrix} \quad (12)$$

$$\mathbf{d} = \mathbf{A} \cdot \mathbf{F} \cdot \mathbf{g}$$

The elements  $L_{ni}$  of the matrix  $\mathbf{L}$  can be determined explicitly from  $\mathbf{F}$  and  $\mathbf{h}$ , but  $L_{ni}$  can also be determined from the following autoregression equation involving the experimental observables  $y_k$  and perturbations  $w_k$ :

$$y_k = a_1 y_{k-1} + a_2 y_{k-2} + \dots + a_n y_{k-n} + b_0 + b_1 w_{k-1} + b_2 w_{k-2} + \dots + b_n w_{k-n} \quad (13)$$

It can be shown<sup>22</sup> that

$$L_{n1} = a_n, \quad L_{n2} = a_{n-1}, \quad \dots, \quad L_{nn} = a_1 \quad (14)$$

and that the elements of  $\mathbf{d}$  are related to the coefficients of eq 13 by

$$\mathbf{d} = \mathbf{C}^{-1} \cdot \mathbf{b} \quad (15)$$

where

$$\mathbf{C} = \begin{pmatrix} 1 & 0 & 0 & \dots & 0 \\ -a_1 & 1 & 0 & \dots & 0 \\ -a_2 & -a_1 & 1 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ -a_{n-1} & -a_{n-2} & -a_{n-3} & \dots & 1 \end{pmatrix} \quad (16)$$

$$\mathbf{b} = \begin{pmatrix} b_1 \\ b_2 \\ b_3 \\ \vdots \\ b_n \end{pmatrix}$$

In an experimental investigation,  $\mathbf{F}$  and, consequently,  $\mathbf{A}$  are usually unknown. The coefficients  $a_i$  and  $b_i$  in eq 13 can be identified from time series. The matrices  $\mathbf{L}$  and  $\mathbf{C}$  are determined by these coefficients, and  $\mathbf{h}$  and  $\mathbf{g}$  are defined by the experimental conditions. We see from eqs 12 and 15 that  $\mathbf{A}$  must satisfy the equation  $\mathbf{A} \cdot \mathbf{F} \cdot \mathbf{g} = \mathbf{C}^{-1} \cdot \mathbf{b}$ . By carrying out perturbation experiments with  $n$  linearly independent vectors  $\mathbf{g}$  and determining the corresponding vectors  $\mathbf{b}$ , the following matrix equation can be established:

$$\mathbf{A} \cdot \mathbf{F} \cdot \mathbf{G} = \mathbf{C}^{-1} \cdot \mathbf{B} \quad (17)$$

where  $\mathbf{G} = (\mathbf{g}_1, \dots, \mathbf{g}_n)$  and  $\mathbf{B} = (\mathbf{b}_1, \dots, \mathbf{b}_n)$ . Introducing

$$\Phi = \mathbf{A} \cdot \mathbf{F} = \mathbf{C}^{-1} \cdot \mathbf{B} \cdot \mathbf{G}^{-1} \quad (18)$$

the  $\mathbf{F}$  matrix can be determined from

$$\mathbf{F} = \Phi^{-1} \cdot \mathbf{L} \cdot \Phi \quad (19)$$

provided the matrix  $\Phi$  is invertible. Consequently

$$\mathbf{J} = \mathbf{V} \cdot \log(\mathbf{A}) \cdot \mathbf{V}^{-1} \frac{1}{\Delta t} \quad (20)$$

where  $\mathbf{V}$  is a matrix of right eigenvectors of  $\mathbf{F}$  and  $\mathbf{A}$  is a diagonal matrix of corresponding eigenvalues. The  $\Phi$  matrix corresponds to the coordinate transformation from the concentration space of eq 10 to the "canonical" space of eq 11.

For many chemical systems, some of the modes are too fast to be observed, and therefore the states that are actually observed are essentially confined to a  $p$  dimensional subspace, where  $p < n$ . In this case, eq 19 can no longer be used directly, since  $\Phi$  becomes ill-conditioned. The problem can be traced back to a degeneracy arising in the autoregression model (13). Partial extraction of information about  $\mathbf{F}$  is still possible, however. We assume that the eigenvalues of  $\mathbf{F} = e^{\mathbf{J}\Delta t}$  can be separated into two groups,  $\rho_i$  and  $\rho_j$ , where  $i = 1 \dots p$  and  $j = p + 1 \dots n$ , such that  $|\rho_i| \gg |\rho_j|$ . The first group corresponds to the slow modes, while the second group corresponds to the fast modes.

The autoregression model, identified from the motion in the slow subspace, will have a reduced order of  $p$ , and, correspondingly, matrices  $\mathbf{L}$  and  $\mathbf{C}$  will become  $p \times p$ . However, we can still perform  $n$  experiments with  $n$  perturbing species, obtaining the full rank  $n \times n$  matrix  $\mathbf{G}$  and  $p \times n$  matrix  $\mathbf{B}$ . Equation 18 is still well-defined in this case, but  $\Phi$  becomes a rectangular  $p \times n$  matrix and does not provide a one-to-one correspondence between the canonical space and the concentration space. If we represent the canonical transition matrix  $\mathbf{L}$  through its left eigenvectors  $\mathbf{U}$ , where  $\mathbf{L} = \mathbf{U}^{-1} \cdot \mathbf{A} \cdot \mathbf{U}$  (and  $\mathbf{A}$  is now  $p$  dimensional), then we can obtain the left eigenvectors  $\mathbf{W}$  for the slow modes by using the coordinate transformation provided by  $\Phi$ :

$$\mathbf{W} = \mathbf{U} \cdot \Phi \quad (21)$$

The left eigenvectors for the slower (measurable) modes are recovered by this method. If all of the modes are measurable, we recover the full set of left eigenvectors, and by inversion of the matrix of the left eigenvectors we obtain the full set of right eigenvectors. Knowing both the left and right eigenvectors, together with the corresponding eigenvalues, allows us as in eq 20 to determine the transition matrix for the discrete model

and the corresponding Jacobian matrix for the continuous model. If  $m$  modes are so fast that their dynamics cannot be recovered, we assign zero eigenvalues to these modes (where zero eigenvalues of the transition matrix correspond to infinitely large negative eigenvalues of the Jacobian). We can still determine the left eigenvectors for the slower modes, as previously described. However, we do not obtain a complete set and thus we cannot use matrix inversion to obtain the unique right eigenvectors.

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