

Review

SENSITIVITY ANALYSIS OF COMPLEX KINETIC SYSTEMS. TOOLS AND APPLICATIONS

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Abstract

Sensitivity analysis investigates the effect of parameter change on the solution of mathematical models. In chemical kinetics, models are usually based on differential equations and the results are concentration-time curves, reaction rates, and various kinetic features of the reaction. This review discusses in detail the concentration sensitivity, rate sensitivity, and feature sensitivity analysis of spatially homogeneous constant-parameter reaction systems. Sensitivity analyses of distributed parameter systems and of stochastic systems are also briefly described. Special attention is paid to the interpretation of sensitivity coefficients which can provide information about the importance and interconnection of parameters and variables. Applications of sensitivity analysis to uncertainty analysis, parametric scaling, parameter estimation, experimental design, stability analysis, repro-modeling, and investigation and reduction of complex reaction mechanisms are discussed profoundly.

1. Introduction

Complex mathematical models have been used from the very beginnings of reaction kinetics for the description of dynamic phenomena. The greatest practical problem, the numerical solution of stiff differential equations, was solved in the early seventies, and then new questions were raised: What is the nature of the connections between solution and parameters and would it not be possible to describe the phenomena by fewer parameters? These are the topics of sensitivity analysis. In the last fifteen years, the theory of sensitivity analysis became very widespread and its practical usefulness was demonstrated in many fields.

In a number of recent papers dealing with the art of kinetic modeling, sensitivity analysis is discussed more [1,2] or less [3-7] profoundly. The single comprehensive review on sensitivity analysis was written by Rabitz et al. [8] and appeared in 1983.

Since that time, new concepts appeared as a result of the rapid development of sensitivity theory. There are several reviews on the various subfields of sensitivity analysis: Tilden et al. overviewed the local and global methods [9], Cukier et al. summarized the FAST method [10], and other non-comprehensive reviews can also be found in the literature [11–17].

Sensitivity methods developed for the study of spatially homogeneous constant-parameter reaction systems are discussed in section 2. Other methods, described in section 3, are suitable for the calculation of the sensitivity of special systems which occur when the kinetic model has space- and time-dependent parameters or when the kinetics is described by a stochastic or by a network model, or when experimental data are processed. The numbers obtained by the sensitivity methods have to be converted into chemical knowledge by the interpretation of sensitivity information (section 4). Nowadays, diverse advanced software (listed in section 5) is available for those who wish to use the above described *tools* of sensitivity analysis. The *applications* of the theory are described in detail in section 6.

In this review, sensitivity analysis will be discussed from the point of view of reaction kinetics. Mathematical tools used in sensitivity theory are usually not new, and some computational methods have even appeared in engineering science [18,19]. In this paper, the first appearance of methods in chemical kinetics is cited, but their mathematical and engineering roots are not searched. Such references can be found in the original papers and in refs. [8] and [9].

Sensitivity methods elaborated primarily for reaction kinetics can usually be used without changes in other fields where dynamic models described by differential equations are applied. However, application of the theory in other disciplines is not discussed here. A large part of the sensitivity methods used in the investigation of complex mechanisms was also applied to molecular dynamics. Although molecular dynamics and chemical kinetics are related disciplines, applications of sensitivity analysis in those fields will not be cited here, and the reader is referred to the following reviews: [14], [20] and [21].

2. Basic sensitivity methods

The kinetics of a spatially homogeneous reaction system is usually modeled by an initial value problem:

$$dc/dt = f(c, k), \quad c(0) = c^0, \quad (1)$$

where c is the n -vector of concentrations and k is the m -vector of system parameters. These parameters may include rate coefficients, Arrhenius parameters, temperature, pressure, etc., but initial concentrations are not considered in vector k . The solutions of the system of ordinary differential equations (1) are concentration–time curves. Rates of production of species can also be calculated from concentrations. Often,

certain kinetic features of the modeled systems, deduced from concentration curves, are more important for the investigator than the concentration–time curves themselves. Sensitivity analysis can be classified on the basis of the output of the kinetic model investigated as a function of parameters. Thus, concentration sensitivity, rate sensitivity, various feature sensitivities, etc. may be distinguished. Sensitivity methods may be divided from another point of view as well. Local methods refer to the small changes of parameters, while global methods refer to the effect of simultaneous, possibly orders-of-magnitude parameter changes.

2.1. LOCAL CONCENTRATION SENSITIVITIES

The effect of a parameter change on the solution can be expressed by a Taylor series expansion:

$$c_i(t, \mathbf{k} + \Delta \mathbf{k}) = c_i(t, \mathbf{k}) + \sum_{j=1}^m \frac{\partial c_i}{\partial k_j} \Delta k_j + \frac{1}{2} \sum_{l=1}^m \sum_{j=1}^m \frac{\partial^2 c_i}{\partial k_l \partial k_j} \Delta k_l \Delta k_j + \dots \quad (2)$$

In this equation, the partial derivatives $\partial c_i / \partial k_j$ are called the *first-order local concentration sensitivity coefficients*, while $\partial^2 c_i / \partial k_l \partial k_j$ are the *second-order local concentration sensitivity coefficients*, etc. Usually, only the first-order (or linear) sensitivity coefficients $\partial c_i / \partial k_j$ are computed and studied. They constitute the *sensitivity matrix S*, which represents a linear approximation of the dependence of the solutions on parameter changes.

Assume that system (1) of ODEs is solved from $t = 0$ to $t = t_1$. Then the parameters are changed by $\Delta \mathbf{k}$ and the solution is continued to t_2 . The difference between the original c and the perturbed c' solutions can be approximated by the sensitivity matrix:

$$c'(t_2) = c(t_2) + S(t_2, t_1) \Delta \mathbf{k}_{t_1} \quad (3)$$

This equation shows that the sensitivity matrices have a double time dependence: $S(t_2, t_1) = \partial c(t_2) / \partial \mathbf{k}(t_1)$. Usually, $t_1 = 0$ is selected. It seems natural to identify the initial time of the ODE solution with the initial time of the sensitivity calculation, but this selection implies a loss of generality. In some cases when, for example, combustion reactions are studied in a batch reactor, there is a natural zero time of reaction (the time of ignition) but, for example in the case of atmospheric chemistry, the selection of t_1 and t_2 is arbitrary.

Matrix S can be obtained by differentiation if the analytical solution of an ODE is known. Unfortunately, in chemical kinetics such simple systems are rarely met and numerical methods have to be applied. In sections 2.1.1–2.1.5, five methods will be described for the numerical calculation of the local concentration sensitivity matrix. The methods are compared briefly in section 2.1.6. In the case of stationary systems, the

limit in time of the sensitivity matrix can be calculated by an algebraic expression (section 2.1.7). Two methods, discussed in sections 2.1.8 and 2.1.9, were developed for for an approximate calculation of the sensitivity matrix.

2.1.1. Brute force method

The simplest way of calculating local concentration sensitivities is the use of the *finite difference approximation*. This technique is also called the *brute force method* or the *indirect method*. Applying this method, the j th parameter is changed at time t_1 by Δk_j , while all other parameters are held fixed. Matrix S is calculated from the difference of the original and perturbed solutions:

$$\frac{\partial c(t_2)}{\partial k_j(t_1)} \approx \frac{c(t_2, k_j + \Delta k_j) - c(t_2, k_j)}{\Delta k_j} \quad j = 1, \dots, m. \quad (4)$$

Equation (4) shows that the application of the brute force method requires the solution of the differential equation (1) using the nominal value of parameters and m solutions of the equation using perturbed parameter sets. The sensitivities obtained belong to the $(k + \Delta k/2)$ parameter set. If the sensitivity coefficients were desired to belong to the nominal parameter set k , eq. (4) should be modified by replacing the second term in the numerator by $c(t_2, k_j - \Delta k_j)$ and the denominator by $2\Delta k_j$ [22–24]. Nevertheless, when using this centered formula, $2m$ solutions are required.

The brute force method is widely used since no extra code beyond the original ODE solver is needed for the calculation of sensitivities. However, this method is not recommended because sensitivity coefficients can be calculated consuming much less computer time by other methods, e.g. the direct method [23,24]. Moreover, the estimation of the errors of sensitivity coefficients calculated by eq. (4) requires at least as much computer time as the calculation itself. The errors can be minimized by an appropriate selection of Δk_j (see [8], p. 422). If Δk_j is large, the linearity of approximation fails, but if Δk_j is too small, the round-off error is high.

Very often, a heuristic sensitivity measure is obtained using eq. (4) by changing the parameters by 50% [25], or by a factor of 2 [26–30] or 5 [31,32,173], respectively. The sensitivity coefficients obtained in this way are neither local nor global sensitivity measures.

2.1.2. Determination of sensitivities using approximate empirical models

The method of Miller and Frenklach [33–35] is based on approximations by empirical models of the solution of system (1) of ODEs in a parameter region at time t . Sensitivity information is obtained by differentiating the empirical equations. The approximation requires much more computational effort than the computation of sensitivities for a single-parameter set. It is, however, a good investment if a parameter

estimation procedure requires the knowledge of sensitivities at several points of a parameter region. Approximate values of local sensitivity coefficients belonging to these points can be calculated from the obtained $S(k)$ functions, but significant differences may occur between the exact and approximated sensitivity coefficients.

A similar procedure was also applied by Derwent and Hov [36].

2.1.3. Direct method

Differentiation of eq. (1) with respect to k_j yields the following set of sensitivity differential equations [37]:

$$\frac{d}{dt} \frac{\partial c}{\partial k_j} = \mathbf{J}(t) \frac{\partial c}{\partial k_j} + \frac{\partial f(t)}{\partial k_j}, \quad (5)$$

where $\mathbf{J}(t) = \partial f / \partial c$ and the initial condition for $\partial c / \partial k_j$ is a zero vector.

A number of methods for computing the local concentration sensitivity coefficients are based on eq. (5). The three strategies described in this section are commonly referred to as the *direct method*. Other, more sophisticated, methods proposed for the solution of eq. (5) have different names, such as the Green function method, polynomial approximation method, etc., and they will be treated separately below.

Higher-order sensitivities can be calculated by further differentiation of eq. (5). The generic expression for the calculation of arbitrary-order sensitivities is the following linear differential equation [38]:

$$\dot{\mathbf{w}} = \mathbf{J} \mathbf{w} + \mathbf{s}, \quad (6)$$

where the inhomogeneous term \mathbf{s} is independent of \mathbf{w} . In the case of second-order sensitivities [39]:

$$\mathbf{w} = \partial^2 c / \partial k_i \partial k_j, \quad (7)$$

and

$$\begin{aligned} \mathbf{s} = & \partial^2 f / \partial k_i \partial k_j + (\partial \mathbf{J} / \partial k_i) (\partial c / \partial k_j) + (\partial \mathbf{J} / \partial k_j) (\partial c / \partial k_i) \\ & + \sum_{i=1}^m \sum_{j=1}^m (\partial \mathbf{J}_i / \partial c_j) (\partial c / \partial k_i) (\partial c / \partial k_j), \end{aligned} \quad (8)$$

where \mathbf{J}_i is the i th column of the Jacobian. Since the structure of the differential equations for the higher-order sensitivities is very similar to eq. (5), these higher-order sensitivities can be calculated by most of the methods described below (cf. [12,13,22,38–41]).

Equations (5) and (1) are coupled through matrices $\partial f/\partial c$ and $\partial f/\partial k$, that is, the solution of eq. (5) requires the knowledge of the solution of eq. (1) in all the points where the ODE solver calculates the right-hand side of eq. (5). Connections between these two equations can be made in one of the following ways:

(1) Solve the couple of equations (1) and (5) for $j = 1, \dots, m$, which requires the solution of $2n$ ODEs m times [42]. This version is the simplest to code, but is the least economical and may cause numerical difficulties [43–45].

(2) The solutions of systems (1) and (5) can be decoupled. First, differential equation (1) is solved and the concentration–time curves obtained are stored in a table. Concentration values desired for the solution of eq. (5) at times when there is no tabulated value are obtained by interpolation [12,45,46].

An improved version of the *decoupled direct method* was presented by Dunker [22,23]. He called attention to the fact that eqs. (1) and (5) have the same Jacobian, therefore a stiff ODE solver will use the same step size and order of approximation in the solution of eqs. (1) and (5). His method first manages a step for the solution of eq. (1), and also performs steps for the solution of eq. (5) for $j = 1, \dots, m$. The procedure is repeated in the next step. This approach is applicable only in the case where the ODE solution method is fully implicit. Since the Jacobians of the equations are the same, it has to be triangularized only once for each time interval.

Dunker's implementation was based on the numerical integration program LSODE of Hindmarsh. Recently, a new coding of this algorithm, also based on the LSODE program, was elaborated by Leis and Kramer [47,48]. Their previous realization was based on the program LSODI, which was valid only for restricted systems of differential/algebraic equations [49]. The implementation by Caracotsios and Stewart [50] is written for general systems of differential/algebraic equations. Their work is based on the code DASSL.

(3) Solve eq. (1) and eq. (5) for all $j = 1, \dots, m$ simultaneously, which requires the solution of $(m+1)n$ ODEs. Since implicit or semi-implicit algorithms appropriate for solving stiff differential equations require the decomposition of the $(m+1)n \times (m+1)n$ Jacobian in each step, the direct solution of this large system of ODEs is inefficient. However, Dickinson and Gelinas [42] called attention to the fact that this large Jacobian has an almost block-diagonal structure, and Valkó and Vajda [51] constructed a fast algorithm – called the *decomposed direct method* – for the efficient solution of this large system of ODEs. Similarly to the method of Dunker, only the Jacobian of eq. (1) has to be decomposed and only once in each step.

The application of the direct method was discussed in refs. [12,22,24,37,38,41–43,45,47,50–63].

2.1.4. The Green function method

Differentiating eq. (1) with respect to initial concentrations c^0 , the following equation is obtained:

$$\frac{d}{dt} \frac{\partial c(t)}{\partial c_i^0(t_1)} = \mathbf{J}(t) \frac{\partial c(t)}{\partial c_i^0(t_1)} \quad i = 1, \dots, n, \quad (9)$$

where t_1 is the initial time of sensitivity calculation and $\partial c(t_1)/\partial c_i^0(t_1) = \delta_i$. The symbol δ_i represents a vector of zeroes except in the i th position, where it has 1. Rewriting this equation in terms of the matrix formalism, one obtains:

$$\frac{d}{dt} \mathbf{K}(t, t_1) = \mathbf{J}(t)\mathbf{K}(t, t_1), \quad (10)$$

where \mathbf{K} is the *initial concentration sensitivity matrix*. $\mathbf{K}(t, t_1) = \{\partial c_i(t)/\partial c_j^0(t_1)\}$, with $\mathbf{K}(t_1, t_1) = \mathbf{I}$ and $t \geq t_1$.

Since eq. (5) is a linear inhomogeneous equation with time-dependent coefficients, it can be solved by first calculating the solution of the homogeneous part (eq. (10)) and then determining the particular solutions corresponding to each parameter:

$$\frac{\partial c(t_2)}{\partial k_j(t_1)} = \int_{t_1}^{t_2} \mathbf{K}(t_2, s) \frac{\partial f(s)}{\partial k_j} ds. \quad (11)$$

In the above equation, \mathbf{K} is known as the *Green function matrix* or *kernel*. The sensitivity method that is based on eq. (11) is named the *Green function method*. This technique is also called the *variational method*. It was first applied to solve problems in chemical kinetics by Rabitz et al. [39]. There are several variants of the Green function method and they differ from each other in the calculation of the matrix \mathbf{K} :

(1) Equation (11) requires \mathbf{K} as the function of the second argument, and this matrix can be determined via the calculation of the adjoint Green function \mathbf{K}^\dagger using the identities $\mathbf{K}^\dagger(t_1, t) = \mathbf{K}(t, t_1)$ and $\mathbf{K}(t_3, t_1) = \mathbf{K}(t_3, t_2)\mathbf{K}(t_2, t_1)$. The adjoint Green function is obtained by the solution of the following differential equation:

$$\frac{d}{dt} \mathbf{K}^\dagger(t_1, t) = -\mathbf{K}^\dagger(t_1, t)\mathbf{J}(t), \quad (12)$$

where $\mathbf{K}^\dagger(t, t) = \mathbf{I}$ and $t_1 \leq t$.

(2) The Green function for $t \geq t_1$ can also be expressed as

$$\mathbf{K}(t, t_1) = \mathbf{G}(t) \mathbf{G}^{-1}(t_1), \quad (13)$$

where

$$d/dt \mathbf{G}(t) = \mathbf{J}(t) \mathbf{G}(t); \quad \mathbf{G}(t_0) = \mathbf{I}. \quad (14)$$

The matrix \mathbf{G} is not invertible numerically in all cases [39], but Hwang proposed a solution for this problem [40]. His algorithm investigates the determinant of the matrix \mathbf{G} during the solution of eq. (14) and when the value of $|\det \mathbf{G}|$ goes below a certain bound, the calculation of \mathbf{G} is restarted. The procedure divides the time interval into parts; in other words, it rescales it. The matrix \mathbf{G} is given as a product of matrices \mathbf{G}' calculated in the subintervals. This variant of the Green function method – called the *scaled Green function method* – was elaborated in two versions: in the first version, called the SGFM/I method, the rescaling is done when a numerical singularity of \mathbf{G} is detected [40]. According to the second version (SGFM/II), rescaling is carried out at the beginning of each step in the numerical integration of eq. (14) [64,65] and the exponential character of \mathbf{G} is also taken into account [66].

(3) Rabitz et al. introduced the *analytically integrated Magnus* version of the Green function method [45]. In the GFM/AIM method, the piecewise Magnus method is applied, i.e. matrix \mathbf{K} is approximated by a matrix exponential:

$$\mathbf{K}(t + \Delta t, t) = \exp \int_t^{t + \Delta t} \mathbf{J}(s) ds. \quad (15)$$

The sensitivities are then calculated from the kernel by analytical approximations to the corresponding integral. The GFM/AIM method was found to be several times faster than the original Green function method [12].

In all the Green function methods, the numerical effort is proportional to the number of variables and not to the number of parameters. The Green function method is particularly suitable if the sensitivities of one concentration to several parameters are to be determined. In this case, the total effort is in the order of one kinetic solution. However, the algorithms of the Green function methods are very involved, requiring not only the solution of stiff differential equations but also interpolation of functions, integration using quadratures, and matrix operations. These are hardly controllable sources of numerical errors.

The Green function matrix technique was extended to provide the sensitivities of objective functions [67,68].

Useful advice for the computational implementation of the Green function method (version (1)) is given in [69]. Edelson et al. coded the Green function algorithm for a vector machine [70]. The Green function method was applied to solve kinetic problems in a number of papers [12,15,22,39,40,43–45,64,66–68,70–88].

2.1.5. The polynomial approximation method

The *polynomial approximation method* elaborated by Hwang [38] transforms the sensitivity differential equations (5) to a set of algebraic ones. The original time interval is divided into subintervals. The variation of sensitivity coefficients with time is approximated by Lagrange interpolation polynomials of degree L :

$$\frac{\partial c(t)}{\partial k_j} \sum_{s=0}^L l_s(t) \frac{\partial c}{\partial k_j}(t_s); \quad j = 1, 2, \dots, m. \quad (16)$$

The value of $\partial c/\partial k_j$ is known at t_0 and the values of $\partial c/\partial k_j$ for L prescribed times ($t_0 < t_1 < \dots < t_L$) are determined by requiring that eq. (16) satisfy eq. (5) at these points. This condition can be expressed by an algebraic equation [38] and the values are given by its solution.

Information is needed for the appropriate division of the time domain and therefore a preliminary study of the behavior of eq. (1) is necessary, which makes the polynomial approximation method slightly uncomfortable. However, as in the case of the Green function method, the main computational effort is proportional to the number of species and not to the number of parameters. Hwang demonstrated the high computational speed and good numerical stability of the method. A computational algorithm and a FORTRAN code list were also provided [89]. The method was extended to spatially inhomogeneous systems, too [1].

2.1.6. Which method to choose?

There are a number of articles (cf. [12,22,24,38,43,45,47,51]) in which the above discussed methods are compared. The conclusion of each article is that the authors' own method is faster and maybe more accurate than the previously published methods. Indeed, the methods are different from each other in accuracy and computer time requirements, but these characteristics may be different for different problems. The improved direct methods seem to provide highly accurate sensitivities and they consume relatively little computer time; therefore, the use of such methods is recommended in general. If the number of parameters is large in comparison with the number of state variables, the use of the GFM/AIM method or that of the polynomial approximation method is advisable.

2.1.7. Stationary systems

In equilibrium and in stationary state, concentrations are constant. Sensitivity coefficients are, however, dynamic quantities governed by eq. (5). The time profiles of the sensitivity coefficients give the dynamic response of the system to a differential change in k_j (see the analytical expression in [8], p. 426), and the *stationary sensitivity coefficients* are the limits in time of the dynamic quantities [46]. (This latter statement is valid only if the steady state is asymptotically stable.) For stationary conditions, species concentrations as well as matrices J and F are time invariant; thus, the stationary sensitivity coefficients may be obtained from algebraic equations:

$$\left(\frac{\partial c}{\partial k_j} \right) = -J^{-1} F_j, \quad j = 1, \dots, m, \quad (17)$$

where \mathbf{J} is the Jacobian and \mathbf{F}_j is the j th column of matrix $\mathbf{F} = \{\partial f_i / \partial k_j\}$. Equation (17) follows from eq. (5) by taking the left-hand sides equal to zero.

The stationary sensitivity matrix represents the change of stationary species concentrations as a result of a differential change in parameters. This sensitivity measure is well applicable in the parameter estimation of stationary kinetic systems [90].

2.1.8. Quasi-stationary sensitivity

All sensitivity coefficients are zero at t_1 (according to the initial condition of the sensitivity equation (5)), and they usually change very rapidly only in a short time interval. An experience of numerical calculations is that at times $t_2 \gg t_1$, the change of local concentration sensitivities is not dramatic unless the change of concentrations is rapid. This behavior is similar to the change of the concentrations of free radicals having a short lifetime. This fact gave the idea to approximate local concentration sensitivities with *quasi-stationary sensitivities*:

$$\partial c_i(t_2) / \partial k_j(t_1) \approx s_{ij}^q(t_2); \quad t_1 \ll t_2. \quad (18)$$

The structure of sensitivity differential equations (5) allows the use of the Tihonov theorem [91], and quasi-stationary sensitivities can be calculated by an algebraic equation:

$$\mathbf{0} = \mathbf{J} \mathbf{S}^q + \mathbf{F}, \quad (19)$$

$$\mathbf{S}^q = -\mathbf{J}^{-1} \mathbf{F}. \quad (20)$$

The matrix \mathbf{S}^q is a poor approximation of the sensitivity matrix \mathbf{S} , yet it can be successfully applied to reveal important reactions in complex reactions systems [91].

2.1.9. Scaling relations and self-similarity conditions

Another way of approximately calculating sensitivity coefficients is based on the observation that the shapes of calculated sensitivity curves are in most cases very similar to each other. This is usually the case when a dependent variable plays a dominant controlling role in the kinetics. Such a dominant variable (denoted by c_1) might be a radical concentration or the temperature in flame systems. The controlling role can be formulated by

$$c_i(t, \mathbf{k}) \approx F_i(c_1(t, \mathbf{k})) \quad i \neq 1. \quad (21)$$

The functional dependence between concentrations (variables) leads to the *scaling relations* [14,92] between sensitivities:

$$\partial c_i(t_2)/\partial k_j(t_1) = (\partial c_i(t_2)/\partial k_j(t_1)) (f_i(t_2)/f_1(t_2)). \quad (22)$$

A consequence of these relations is that sensitivity coefficients fulfill the *self-similarity condition*:

$$\partial c_i(t_2)/\partial k_j(t_1) = \lambda_i(t_2) \sigma_j(t_1), \quad (23)$$

where the characteristic constants σ_j scale the sensitivity coefficients for a given dependent variable with respect to the various parameters.

Both the scaling and self-similarity relations were elaborated for space-time systems [14,61,92,93]. Similar equations can be derived for multidominant dependent variable systems.

2.2. GLOBAL CONCENTRATION SENSITIVITY

In global methods, the parameter vector \mathbf{k} is considered to be a random vector with probability density function p . Therefore, the solutions of the models such as, for instance, the concentrations, are also random variables at any time. The methods of *global concentration sensitivity analysis* determine the mean and the variance or the probability density function of concentrations, given the probability density function of parameters and initial concentrations. Usually, the probability density function of parameters is not known, and a presumed probability density function has to be calculated from the known means and variances of parameters by assuming a physically reasonable distribution.

The single non-stochastic global sensitivity method is based on the Lie algebraic and group methods. Nevertheless, the *Lie group method* [94,95,169,170] was only limitedly applied for systems of nonlinear differential equations and therefore this method will not be discussed in detail.

2.2.1. The FAST and the WASP methods

The most widely used global method is the *Fourier amplitude sensitivity test* (FAST) method, which was developed by Cukier et al. [10,96–99].

Assuming that the concentrations are random variables, their mean value at time t is given by

$$\langle c_i(t) \rangle = \int c_i(t, \mathbf{k}) p(\mathbf{k}) d\mathbf{k}, \quad (24)$$

where $p(\mathbf{k})$ is the probability density function of \mathbf{k} . This m -dimensional integral can be converted into an equivalent one-dimensional integral using the following transformations:

$$k_j = G_j(\sin \omega_j s), \quad j = 1, 2, \dots, m, \quad (25)$$

where the functions G_j are unambiguously determined by the probability density function p , ω_j is a frequency which belongs to the j th parameter, and s is a scalar variable called the search parameter. Expression (25) shows that parameter k_j varies as a periodic function of the search variable s . If the frequencies ω_j are incommensurate, the curve defined by eq. (25) fills the m -dimensional parameter space in the range $-\infty < s < +\infty$. For computational reasons, it is practical to use appropriate integer frequencies instead, and therefore the concentrations will be 2π periodic functions of s at time t and they can be Fourier analyzed. The variance of concentration c_i at time t can be expressed by:

$$\sigma_i^2(t) = 2 \sum_{l=1}^{+\infty} (A_{il}^2(t) + B_{il}^2(t)), \quad (26)$$

where $A_{il}(t)$ and $B_{il}(t)$ are the Fourier coefficients:

$$A_{il}(t) = \frac{1}{2\pi} \int_{-\pi}^{\pi} c_i(t, s) \cos ls \, ds, \quad l = 0, 1, \dots; \quad (27)$$

$$B_{il}(t) = \frac{1}{2\pi} \int_{-\pi}^{\pi} c_i(t, s) \sin ls \, ds, \quad l = 1, 2, \dots. \quad (28)$$

If the Fourier coefficients are evaluated with the fundamental frequencies of transformation (25) or with its harmonics ($l = r\omega_j$, $r = 1, 2, \dots$), then the obtained variances

$$\sigma_{ij}^2(t) = 2 \sum_{r=1}^{+\infty} (A_{i,r\omega_j}^2(t) + B_{i,r\omega_j}^2(t)) \quad (29)$$

are part of the total variance $\sigma_i^2(t)$ and correspond to the variance of c_i arising from the uncertainty in the j th parameter. The ratio $S_{ij}(t) = \sigma_{ij}^2(t)/\sigma_i^2(t)$, called *partial variance*, is the basic measure of sensitivity in the FAST method. The partial variance matrix is a normed matrix and therefore it is independent of the units used.

The FAST method was generalized by Kanatani [100], and he developed its further mathematical foundations. An algorithmic improvement of the FAST method was proposed in [101].

Contrary to its name, the FAST method requires much computer time. If there are m parameters in the model and they are varied over orders of magnitude, the system of ODEs has to be solved about $N = 1.2 \times m^{2.5}$ times [99]. In the case of a 50-parameter model, this means 21,200 runs.

Computational implementations of the FAST method were reported by Seinfeld et al. [102, 103] and by Pierce et al. [104]. Applications of the FAST method are also found in refs. [9, 10, 52, 97, 101, 104–110].

The point of the FAST method is that the $\{(\cos ns), (\sin ns), n = 0, 1, 2, \dots\}$ set of functions can serve as a basis for the decomposition of the corresponding function $c(s)$. A similar decomposition can be carried out with other functions of similar properties. An example of this was shown by Pierce and Cukier [111], using Walsh functions. The Walsh functions form a complete orthogonal system of two-valued functions.

The *Walsh amplitude sensitivity procedure* (WASP) is very similar to FAST. In the WASP method, the parameters are assumed to have two values with "equal probability", and the effect of parameter change from the first value to the second value on the output is investigated. A practical choice for the parameters is the selection of extreme values, maximum and minimum, of the parameter uncertainty range. Thus, the WASP method provides an upper limit of the model sensitivity with respect to other choices of parameter distribution functions. The WASP method is suitable for studying the effect of a model reduction, i.e. setting zero the value of part of the parameters. In such an investigation, the upper value is the nominal value of the parameter and the lower value is zero. The WASP method is numerically simpler than the FAST method, but consumes much more computer time. The investigation of a 50-parameter model would require $2^{50} \approx 10^{15}$ runs.

2.2.2. Stochastic sensitivity analysis

The method of *stochastic sensitivity analysis* is a global sensitivity method based on the solution of a partial differential equation. This technique was elaborated by Costanza and Seinfeld [9,112]. The name "stochastic sensitivity analysis" is not fortunate, since all the global methods deal with stochastic measures. Moreover, a different technique, for the investigation of gas-surface collisions [113,114], has the same name.

The initial value problem (1) can be reformulated by joining the concentration and parameter space:

$$\dot{x} = F(x); \quad x(0) = x_0, \quad (30)$$

where $F(x) = (f_1, \dots, f_n, 0, \dots, 0)$ and $x_0 = (c_1^0, \dots, c_n^0, k_1, \dots, k_m)$. The joint concentration-parameter probability density function can be obtained by the solution of the following equation:

$$\frac{\partial p}{\partial t} + \nabla(Fp) = 0; \quad p(0, x) = p_0(x), \quad (31)$$

where $p_0(x)$ is the probability density function of x_0 .

This method requires considerable computer time since the numerical effort needed to obtain the desired probability density function is comparable to that required in the FAST method.

2.2.3. Monte Carlo methods and Latin hypercube sampling

All the global methods described previously require complex computer codes. *Monte Carlo methods* do not require special programs, but they also consume considerable computer time. A random number generator is used to select values of parameters in the domain of uncertainty according to their probability density function. The system is then solved for each of the parameter combinations. The computed concentration values are analyzed by standard statistical methods at any given time t .

Using this method, the original ODE solver has to be supplemented by two segments for selecting new parameter values and for a statistical analysis of solutions. The convergence of statistical characteristics has to be checked, say, after every thousand runs. Applications of the Monte Carlo methods are given in [115–117].

The *Latin hypercube sampling* can be considered as an improvement of the Monte Carlo methods. In this procedure, the input parameter sets are not selected randomly, but are planned in advance according to a Latin hypercube. The means, variances and cumulative frequency distributions obtained by Latin hypercube sampling are insignificantly different from those generated by Monte Carlo methods, while the computer time demand is about an order of magnitude less [36,118].

2.3. RATE SENSITIVITY

Investigation of the production rate of species is very important in chemical kinetics and their sensitivity is very informative, too. According to the Young theorem, the derivative of concentration sensitivities with respect to time, $(\partial/\partial t)(\partial c_i(t_2)/\partial k_j(t_1))$ is identical to *rate sensitivities*: $(\partial \dot{c}_i(t_2)/\partial k_j(t_1)) = \partial f_i(t_2)/\partial k_j(t_1)$. Once local concentration sensitivities have been computed, the values of rate sensitivity coefficients are given by the sensitivity differential equation (5):

$$\dot{\mathbf{S}}(t_2, t_1) = \mathbf{J}(t_2)\mathbf{S}(t_2, t_1) + \mathbf{F}(t_2). \quad (32)$$

Rate sensitivity coefficients $\partial f_i/\partial k_j$ supply further mechanistic details about a reaction system which are not inherent in the concentration sensitivity coefficients [77,119].

A particular case of rate sensitivities is obtained when $t_1 = t_2$. Then, $\partial f_i(t_2)/\partial k_j(t_2) = \partial f_i(t_2)/\partial k_j$, which is an element of matrix \mathbf{F} . The matrix \mathbf{F} is an algebraic sensitivity measure in contradistinction to the dynamic sensitivities discussed so far. If \mathbf{k} denotes the vector of rate coefficients, then the log-normalized algebraic rate sensitivity matrix $\tilde{\mathbf{F}}$ can be computed by the following equation [120]:

$$\tilde{\mathbf{F}} = \{\partial \ln f_i / \partial \ln k_j\} = \{\nu_{ij} R_j / f_i\}, \quad (33)$$

where ν is the stoichiometric matrix, R_j is the rate of reaction j , and f_i is the production rate of species i . Thus, an element of matrix $\tilde{\mathbf{F}}$ is the ratio of the rate of

formation or consumption of species i in reaction j and the net rate of concentration change of species i .

The matrix \tilde{F} represents the link between concentration sensitivity analysis and rate-of-production analysis. This matrix can be treated like other sensitivity matrices, as discussed in section 4.2, while the connection between the log-normalized local concentration sensitivity matrix \tilde{S} and matrix \tilde{F} provides a mathematical basis for the use of various forms of reaction rate analyses [120]. The investigation and reduction of complex reaction mechanisms can be based very effectively on the study of the matrix \tilde{F} [120–122, 164, 166, 168].

2.4. FEATURE SENSITIVITY ANALYSIS

Results of kinetic modeling are usually concentration–time curves. However, often certain kinetic features of the investigated systems, which are functions of the concentrations, are more important for the investigator than the concentration–time functions themselves. Such features are, for instance, the maximum concentration of a species, the corresponding reaction time, the length of the induction period, or the period time τ of an oscillating reaction.

Feature sensitivities can be determined approximately by the brute force method [2]. However, since concentration–time curves contain all information about features, feature sensitivities can be calculated from concentration sensitivities and concentrations. The first example of this was given by Edelson and Thomas [81], who derived the following equation (without the correction term Q) for the calculation of the period sensitivities of an oscillating reaction:

$$\frac{\partial \tau}{\partial k_j} = \frac{\partial c_i(t_2)/\partial k_j(t_1) - \partial c_i(t_2 + \tau)/\partial k_j(t_1)}{dc_i(t_2)/dt} + Q. \quad (34)$$

The correction term Q may be negligible in some practical calculations [123, 124]. This correction term tends to zero as $(t_2 - t_1) \rightarrow \infty$, which was shown for the general case [123, 125] and for an explicit form [126].

Larter et al. [82] proposed a different but related equation for the calculation of $\partial \tau / \partial k_j$. They pointed out that the accuracy of the computation depends on the species i selected. Györgyi et al. [57] applied Edelson's treatment for the computation of sensitivities in the time periods from minimum to maximum and from maximum to minimum of the concentration of a species. They also suggested a method to select the most appropriate time t_2 and component i for period sensitivity calculations in order to minimize numerical errors.

Rabitz et al. proposed two methods for the computation of sensitivities of arbitrary features from local sensitivities. According to the first method – called *point-wise feature sensitivity analysis* [127] – the feature in question is characterized by a

mathematical equation and feature sensitivities are derived from it. Equation (34) was obtained in a similar way, and also an equation for the calculation of induction period sensitivities was given in ref. [72]. If the investigated feature is the location t^* of the concentration maximum of species i [8,13,72], the corresponding mathematical equation is

$$\dot{c}_i(\mathbf{k}, t(\mathbf{k}))|_{t=t^*} = 0. \quad (35)$$

Differentiation of eq. (35) with respect to k_j yields:

$$\frac{\partial t^*}{\partial k_j(0)} = \frac{-\partial^2 c_i(t^*)/\partial t \partial k_j(0)}{\partial^2 c_i(t^*)/\partial t^2}. \quad (36)$$

Equation (36) indicates that $\partial t^*/\partial k_j$ is the ratio of the appropriate rate sensitivity coefficient and the second derivative of the concentration c_i with respect to time, which can be calculated from the Jacobian and from the first derivative: $\partial^2 c/\partial t^2 = \mathbf{J}f(c)$.

The second approach – called *force-fit feature sensitivity analysis* [128] – is based on fitting by a least-squares procedure the concentration curve $c_i(\mathbf{k}, t)$ to a chosen function $c_i(\beta, t)$ (where β is the vector of feature parameters) in a time interval $[t_1, t_2]$ containing the features of interest. The coefficient $\partial \beta_i/\partial k_j$ is then obtained as a function of $\partial c(\beta, t)/\partial \beta$ and $\partial c(\mathbf{k}, t)/\partial \mathbf{k}$. This approach was applied in a parameter scaling procedure [76] and in the transformation of an elementary chemical kinetic mechanism to a global mechanism [129].

Note that, unless there is an *a priori* reason for selecting a particular functional form for $c_i(\beta, t)$, finding a suitable function may require significant effort and the first approach is preferable.

Feature sensitivities give a different insight into the operation of a kinetic mechanism than concentration sensitivities do. However, the interpretation of feature sensitivities is not straightforward in general. Recently, artificial intelligence was shown [58] to provide a considerable help in the extraction of kinetic information from feature sensitivities. Most applications of feature sensitivities occur in the fields of oscillating reactions [57,58,71,79,80–82], and of combustion kinetics (mostly using the brute force method) [2,28,72,88,130–132].

3. Sensitivity analysis of special systems

The basic case of kinetic modeling is the deterministic simulation of spatially homogeneous constant-parameter systems. Sensitivity methods devoted to the study of reaction systems described by eq. (1) have been discussed in the previous section. In this section, other sensitivity methods, suitable for the investigation of more special systems, are given.

3.1. FUNCTIONAL SENSITIVITY ANALYSIS

In most kinetic modeling studies, parameters are assumed to be constant. In a number of problems of great practical importance, however, parameters are functions of time and/or space. In models of atmospheric chemistry, rate coefficients of photochemical processes are changing with the intensity of sunshine; also in non-isotherm reactors, rate coefficients are functions of time (and space). If the parameters are functions, the appropriate sensitivity analysis is based on their perturbation by another function using the principles of nonlinear functional analysis. *Functional sensitivity analysis* has been used for a long time in control theory and in computational physics. A necessary and sufficient condition of functional sensitivity analysis is the existence of the Gâteaux differentials of the operators appearing in the problem [133,134]. Operators used in chemical problems are usually "well-behaved" (e.g. parameters are all continuous functions) and therefore special techniques are applicable, too.

In chemical kinetics, Dickinson and Gelinas [42] were the first to face the problem of parameter functions in the study of an atmospheric chemical mechanism. In their model, $k_j(t)$ denoted the rate coefficient function of photochemical reaction j and $g_j(t)$ was an appropriately chosen perturbing function. Functional sensitivities were defined by

$$s_{ij} = \left. \frac{\partial c_i(k_j(t) + \varepsilon g_j(t))}{\partial \varepsilon} \right|_{\varepsilon=0} \quad (37)$$

A similar sensitivity definition was also used by Dunker [23, 135] in the study of an air pollution model.

The sensitivity measure s_{ij} depends on the perturbing function g_j . In the general case, this measure can only be calculated by a procedure similar to the brute force method. Therefore, another functional sensitivity measure that is unambiguous and can be calculated by more sophisticated methods was searched for. The sensitivity measure which meets these requirements was named *sensitivity density* [136]. As a first step, sensitivity densities will be shown as applied for constant-parameter models, since in this case a direct comparison to local concentration sensitivities can be made.

The basic idea of local sensitivity analysis is that a constant parameter k_j is changed to a new value at t_1 (and kept at this new value) and the effect of a parameter change on the concentration of species i is observed at t_2 . The essence of sensitivity densities is that the parameter k_j is perturbed by δk_j just at time t_1 and the response at t_2 is characterized by a functional derivative $\delta c_i / \delta k_j$. The sensitivity density matrix $\mathbf{D}(t_2, t_1) = \{\delta c_i(t_2) / \delta k_j(t_1)\}$ can be simply evaluated if the initial concentration sensitivity matrix $\mathbf{K}(t_2, t_1) = \{\partial c(t_2) / \partial c^0(t_1)\}$ and the matrix $\mathbf{F}(t_1) = \{\partial f(t_1) / \partial k\}$ are known:

$$\mathbf{D}(t_2, t_1) = \mathbf{K}(t_2, t_1) \mathbf{F}(t_1). \quad (38)$$

The relation to the local concentration sensitivities is given (for the case of constant parameters) by an integral:

$$S(t_2, t_1) = \int_{t_1}^{t_2} D(t_2, t') dt'. \quad (39)$$

Note that when the sensitivity densities are integrated according to eq. (39) to give local concentration sensitivities, the Green function method is regained. The sensitivity density matrix can also be related [120] simply to the algebraic rate sensitivity matrix. As is apparent from eq. (38), the matrix F is a limit in time of the sensitivity density matrix D :

$$F(t_2) = \lim_{t_1 \rightarrow t_2} D(t_2, t_1). \quad (40)$$

Based on sensitivity densities, a parallel local sensitivity analysis theory for the investigation of constant parameter models can be elaborated. Higher-order sensitivity densities [137], derived sensitivity densities (see section 4.2.2) [138, 139], sensitivity densities of objective functions [67], and experimental sensitivity densities (see section 3.4) [8] were also calculated. However, in the investigation of constant parameter models, sensitivity densities have played only a minor role so far [82].

The use of sensitivity densities is of basic importance in the study of models with space- and time-dependent parameters. Concentration changes in a spatially inhomogeneous chemical system can be described by a set of coupled non-linear partial differential equations:

$$\partial c_i / \partial t = \nabla u(x, t) c_i + \nabla D_i(x, t) \nabla c_i + f(c, k(x, t)) + S_i(x, t) \quad i = 1, \dots, n, \quad (41)$$

with initial and boundary conditions:

$$c_i(0, x) = c_i^0(x), \quad (42)$$

$$A_i^1(x, t) \nabla c_i + A_i^2(x, t) c_i = A_i^3(x, t), \quad (43)$$

where the x space coordinate vector is an element of the space domain \mathcal{D} , $u(x, t)$ is the advection speed field, $D_i(x, t)$ is the matrix of physical or turbulent diffusion, $f(c, k(x, t))$ is the right-hand side of the kinetic differential equation with space- and time-dependent parameters due to space- and time-dependent temperature and/or light flux, and $S_i(x, t)$ represents the sources and sinks of the species in the system.

Sensitivity equations have so far been derived only for a special case of the above problem:

$$\partial c_i / \partial t = \nabla D_i(x, t) \nabla c_i + f(c, k(x, t)) \quad i = 1, \dots, n, \quad (44)$$

$$c_i(0, x) = c_i^0(x), \quad (45)$$

$$A_i^1(x, t) \nabla c_i + A_i^2(x, t) c_i = A_i^3(x, t). \quad (46)$$

An appropriate sensitivity measure for an inhomogeneous reaction system is the generalized sensitivity density:

$$D(x_2, t_2, x', t') = \{ \delta c_i(x_2, t_2) / \delta k_j(x', t') \}. \quad (47)$$

It is a response function which gives the linear response of the concentration of species i at (x_2, t_2) to a small variation in the parameter k_j at (x', t') . The change in the concentration $c_i(x, t_2)$ due to a small variation of $k \rightarrow k + \delta k$ in the parameters is:

$$\delta c(x, t_2) = \int_{t_1}^{t_2} \int_D D(x', t', x, t_2) \delta k(x', t') dx' dt'. \quad (48)$$

Functional derivatives for the study of reaction-diffusion systems were first computed by Koda et al. [52,140]. Rabitz and coworkers showed [136,137,141,142] how a sensitivity analysis of the system described by eqs. (44)–(46) has to be carried out. They introduced the generalized initial concentration sensitivity matrix K (this is also called the Green function):

$$K(x, t, x', t') = \{ \delta c_i(x, t) / \delta c_j(x', t') \}. \quad (49)$$

This measure gives the linear response of the concentration of species i at (x, t) if the concentration of species j is perturbed by $\delta_j \delta(t - t') \delta(x - x')$ at (x', t') . This concentration response function plays a central role in functional sensitivity analysis since all other response functions can be calculated from it.

Expressions for derived sensitivity densities [138,139], higher-order sensitivity densities [137], and for the sensitivity of objective functionals [143] are also given for reaction-diffusion systems.

Frequently, the space and time dependences of parameters are given by functions with constant parameters. Incorporating these functions into the system of differential equations, the resulting, more involved system, has only constant parameters. For example, in the model of a non-isotherm reaction, rate coefficients are functions but Arrhenius parameters are constant values.

If the parameters of a reaction-diffusion system are not space-time dependent, the non-functional sensitivities can be calculated by the methods described in section 2. Such examples are given in refs. [1,41,52,55,93].

3.2. INVESTIGATION OF STOCHASTIC MODELS

In order to take into consideration the randomness of the molecular events responsible for chemical reactions, the concentrations have to be represented by stochastic variables. In macroscopic systems, the fluctuations are often negligible and the deterministic kinetic equations provide an accurate description of the behaviour of the concentrations. In such systems, the fluctuations are important if chemical instabilities exist which lead to the amplification of fluctuations. In the description of chemical reactions involving a small number of molecules inside a small volume, as in the case of reactions in micelles or cells, the stochastic handling of kinetics is essential.

The use of stochastic differential equations is a convenient way for the description of concentration fluctuations in chemical kinetics. These equations differ from the deterministic ones in a noise term:

$$d\rho/dt = f(\rho, k) + P\xi^T; \quad \rho(0) = \rho^0, \quad (50)$$

where ρ is the stochastic vector of concentrations, ξ is a delta correlated Gaussian stochastic variable vector (white noise), and the matrix P is determined by the reaction mechanism and by the volume of the system. All the information on the stochastic variable ρ is summarized in the multiple time probability distribution function $p_n(c_1, t_1; \dots; c_n, t_n)$. This multi-variable function is difficult to look over and the concentration fluctuations can be characterized by other measures which can be calculated from p_n . Such measures (denoted jointly by $F[\rho_i]$) are, for instance, the expected value and the variance of $\rho_i(t)$. Concentration fluctuations can also be characterized by the deviation from the deterministic value $f_i(t) = \rho_i(t) - c_i(t)$ and by the correlation of such deviations: $C_{ij}(t_1, t_2) = \langle f_i(t_1) f_j(t_2) \rangle$.

All of the above functions depend on the parameters and initial concentrations of the kinetic system, and a sensitivity analysis of these functions was elaborated by Dacol and Rabitz [144]. They gave analytical expressions for the evaluation of the local sensitivity and the sensitivity density of the probability distribution function, $\partial p_n / \partial k_j$ and $\delta p_n / \delta k_j$. Calculations of $\partial \langle F[\rho_i] \rangle / \partial k_j$ and $\delta \langle F[\rho_i] \rangle / \delta k_j$ are possible from the former sensitivity functions.

In the case of more involved systems, only numerical calculation of ρ_i is possible. Therefore, a different way was presented for the numerical calculation of $\partial \langle F[\rho_i] \rangle / \partial k_j$ and $\delta \langle F[\rho_i] \rangle / \delta k_j$.

Applying a quasi-linear approximation in the reciprocal volume, Dacol and Rabitz obtained closed expressions for $\langle \rho_i(t) \rangle$ and $\langle \rho_i(t_1) \rho_j(t_2) \rangle$ as well as for their sensitivity coefficients and densities in terms of the deterministic concentrations c and the (deterministic) initial concentration sensitivity matrix K . These expressions allow an investigation of fluctuation phenomena without stochastic simulation. However, this quasi-linear approximation is applicable only in macroscopic systems and far from chemical instability.

3.3. REACTION NETWORK SENSITIVITY ANALYSIS

The network analysis as developed by Clarke reparametrizes the kinetic differential equations using new parameters j and h instead of rate coefficients. The components of the parameter vector j represent the weights assigned to elementary flows in the reaction network, while the parameter vector h can be interpreted as the reciprocal steady state of concentrations. Network analysis relates the dynamics of complex chemical reaction systems to feedback loops in the reaction network.

A combination of network theory and sensitivity analysis, presented by Larter and Clarke [83], investigates the sensitivity of concentrations on the change of new parameters. The new sensitivity matrices $\partial c/\partial j$ and $\partial c/\partial h$ carry information on the effect of these new parameters, as well as on their relative importance and interconnection. As an example, the Brusselator was analyzed [83] and the period sensitivities of the new parameters were studied.

3.4. EXPERIMENTAL SENSITIVITY ANALYSIS

In sensitivity analysis, parameters are considered as the input of models. However, in a parameter estimation procedure the experimental results are the input and the estimated parameters are the output. The *experimental elementary sensitivities*, $E = \{\partial k_j/\partial c_i^e\}$ show how the estimated parameters change when the experimentally measured concentrations c^e change. (One could use any experimental observable instead of concentrations.)

Parameters are usually determined by a least-squares procedure, i.e. by minimizing the function

$$Q = \sum_{i=1}^{n_e} (1 - c_i/c_i^e)^2, \quad (51)$$

where n_e is the number of experimental data and c_i is the i th calculated concentration corresponding to the i th measured concentration c_i^e . From eq. (51), a simple procedure [145,87] yields the following expression for the calculation of log-normalized experimental sensitivities:

$$\sum_{l=1}^{m'} M_{jl} (\partial \ln k_l / \partial \ln c_h^e) = -L_{jh}, \quad j = 1, \dots, m', \quad (52)$$

where m' is the number of estimated parameters,

$$M_{jl} = \sum_{i=1}^{n_e} \{ (\partial^2 \ln c_i / \partial \ln k_j \partial \ln k_l) (c_i/c_i^e) (1 - c_i/c_i^e) + (1 - 2c_i/c_i^e) (c_i/c_i^e) (\partial \ln c_i / \partial \ln k_j) (\partial \ln c_i / \partial \ln k_l) \} \quad (53)$$

and

$$L_{jh} = (1 - 2c_h/c_h^e)(c_h/c_h^e)(\partial \ln c_h / \partial \ln k_j). \quad (54)$$

Equation (52) represents a system of n_e linear inhomogeneous equations and its solution requires the prior calculation of the corresponding first- and second-order local concentration sensitivity coefficients.

Experimental sensitivities can be used to identify parameters which are highly sensitive to noise in the experimental data. These sensitivity coefficients also appear in expressions for parameter deviation arising from uncertainties in and discrepancies between model and measured observables [145].

4. Interpretation of sensitivity information

4.1. IMPORTANCE AND INTERDEPENDENCE OF PARAMETERS

Sensitivity coefficients must have the same physical dimensions or they must be dimensionless if a comparison of them is required. However, the parameters may have different units and then the sensitivity coefficients are directly incomparable. The usual treatment of this problem is to introduce normalized sensitivity matrices [37,43,130]. The elements of the normalized local concentration sensitivity matrix \tilde{S} are dimensionless and therefore their values are independent of the dimensions of the original kinetic model:

$$\tilde{S} = \{(k_j/c_i) (\partial c_i(t_2)/\partial k_j(t_1))\} = \{\partial \ln c_i(t_2)/\partial \ln k_j(t_1)\}. \quad (55)$$

These coefficients represent the percentage change in concentration c_i caused by a percentage change of k_j .

The study of a normalized sensitivity matrix allows one to determine the rank order of parameters on the basis of the effect on c_i at time t_2 as a result of a small parameter change at time t_1 . In the case of another species or different times, a different rank order can be obtained.

Frequently, one is interested in the effect of parameter change on the concentrations of several species. The need for such information has been realized by Edelson [75], and he applied a heuristic measure. Mathematically more established methods can be introduced by using objective functions, which show the deviation of a perturbed solution c_i^* from the nominal solution c_i considering a group of species. Such objective functions are, for instance,

$$e_1 = \sum_{i=1}^{n'} |(c_i^* - c_i)/c_i|,$$

$$e_2 = \sum_{i=1}^{n'} [(c_i^* - c_i)/c_i]^2,$$