Journal of Mathematical Chemistry 5(1990)203–248

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:

$$\mathrm{d}\boldsymbol{c}/\mathrm{d}t = \boldsymbol{f}(\boldsymbol{c}, \boldsymbol{k}), \qquad \boldsymbol{c}(0) = \boldsymbol{c}^0, \tag{1}$$

where $\boldsymbol{c}$ is the n-vector of concentrations and $\boldsymbol{k}$ 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 $\boldsymbol{k}$. 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:

$$c_i(t, \boldsymbol{k} + \Delta \boldsymbol{k}) = c_i(t, \boldsymbol{k}) + \sum_{j=1}^{m} \frac{\partial c_i}{\partial k_j} \Delta k_j + \frac{1}{2} \sum_{l=1}^{m} \sum_{j=1}^{m} \frac{\partial^2 c_i}{\partial k_l \partial k_j} \Delta k_l \, \Delta k_j + \ldots \, . \tag{2}$$

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 $\Delta \boldsymbol{k}$ and the solution is continued to t_2. The difference between the original $\boldsymbol{c}$ and the perturbed $\boldsymbol{c}'$ solutions can be approximated by the sensitivity matrix:

$$\boldsymbol{c}'(t_2) \approx \boldsymbol{c}(t_2) + \mathrm{S}(t_2, t_1) \Delta \boldsymbol{k}_{t_1}. \tag{3}$$

This equation shows that the sensitivity matrices have a double time dependence: $\mathrm{S}(t_2, t_1) = \partial \boldsymbol{c}(t_2) / \partial \boldsymbol{k}(t_1)$. 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 jth 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:

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

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 ($\boldsymbol{k} + \Delta \boldsymbol{k}/2$) parameter set. If the sensitivity coefficients were desired to belong to the nominal parameter set $\boldsymbol{k}$, 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 $\mathbf{S}(\boldsymbol{k})$ 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]:

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

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]:

$$\dot{w} = \mathbf{J}w + s, \tag{6}$$

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

$$w = \partial^2 c/\partial k_i \partial k_j \tag{7}$$

and

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

where $\mathbf{J}_i$ is the ith 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 $j = 1, \ldots, m$, 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 $j = 1, \ldots, m$. 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 $j = 1, \ldots, m$ 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:

$$\frac{\mathrm{d}}{\mathrm{d}t}\frac{\partial \boldsymbol{c}(t)}{\partial c_i^0(t_1)} = \mathbf{J}(t)\frac{\partial \boldsymbol{c}(t)}{\partial c_i^0(t_1)} \qquad i = 1, \ldots, n, \tag{9}$$

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

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

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:

$$\frac{\partial \boldsymbol{c}(t_2)}{\partial k_j(t_1)} = \int_{t_1}^{t_2} \mathbf{K}(t_2, s)\frac{\partial \boldsymbol{f}(s)}{\partial k_j}\,\mathrm{d}s. \tag{11}$$

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:

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

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

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

where

$$\mathrm{d}/\mathrm{d}t\,\mathbf{G}(t) = \mathbf{J}(t)\,\mathbf{G}(t); \qquad \mathbf{G}(t_0) = \mathbf{I}. \tag{14}$$

The matrix **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 **G** during the solution of eq. (14) and when the value of $|\det \mathbf{G}|$ goes below a certain bound, the calculation of **G** is restarted. The procedure divides the time interval into parts; in other words, it rescales it. The matrix **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 **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 **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 **K** is approximated by a matrix exponential:

$$\mathbf{K}(t+\Delta t, t) = \exp \int_{t}^{t+\Delta t} \mathbf{J}(s)\,\mathrm{d}s. \tag{15}$$

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:

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

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 ($t_0 < t_1 < \ldots < t_L$) 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 pubished 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:

$$\left(\frac{\partial c}{\partial k_j}\right) = -\mathbf{J}^{-1}\mathbf{F}_j, \qquad j = 1, \ldots, m, \tag{17}$$

where $\mathbf{J}$ is the Jacobian and $\mathbf{F}_j$ is the jth 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*:

$$\partial c_i(t_2)/\partial k_j(t_1) \approx s^{q}_{ij}(t_2); \qquad t_1 \ll t_2. \tag{18}$$

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:

$$\mathbf{0} = \mathbf{J}\,\mathbf{S}^{q} + \mathbf{F}, \tag{19}$$

$$\mathbf{S}^{q} = -\mathbf{J}^{-1}\mathbf{F}. \tag{20}$$

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

$$c_i(t, \boldsymbol{k}) \approx F_i(c_1(t, \boldsymbol{k})) \qquad i \neq 1. \tag{21}$$

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

$$\partial c_i(t_2)/\partial k_j(t_1) \approx (\partial c_1(t_2)/\partial k_j(t_1))\,(f_i(t_2)/f_1(t_2)). \tag{22}$$

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

$$\partial c_i(t_2)/\partial k_j(t_1) \approx \lambda_i(t_2)\,\sigma_j(t_1), \tag{23}$$

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 $\boldsymbol{k}$ 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

$$\langle c_i(t)\rangle = \int c_i(t, \boldsymbol{k})\, p(\boldsymbol{k})\, \mathrm{d}\boldsymbol{k}, \tag{24}$$

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

$$k_j = G_j(\sin \omega_j s), \qquad j = 1, 2, \ldots, m, \tag{25}$$

where the functions G_j are unambiguously determined by the probability density function p, ω_j is a frequency which belongs to the jth 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:

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

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

$$A_{il}(t) = \frac{1}{2\pi} \int_{-\pi}^{\pi} c_i(t,s) \cos ls \, \mathrm{d}s, \qquad l = 0, 1, \ldots \;; \tag{27}$$

$$B_{il}(t) = \frac{1}{2\pi} \int_{-\pi}^{\pi} c_i(t,s) \sin ls \, \mathrm{d}s, \qquad l = 1, 2, \ldots \;. \tag{28}$$

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

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

are part of the total variance $\sigma_i^2(t)$ and correspond to the variance of c_i arising from the uncertainty in the jth 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 $\{(\cos ns), (\sin ns), n = 0, 1, 2, \ldots\}$ 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:

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

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

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

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):

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

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 $\boldsymbol{k}$ 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]:

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

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 $\tilde{\mathbf{F}}$ 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 $\tilde{\mathbf{S}}$ and matrix $\tilde{\mathbf{F}}$ 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 $\tilde{\mathbf{F}}$ [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:

$$\frac{\partial \tau}{\partial k_j} = \frac{\partial c_i(t_2)/\partial k_j(t_1) - \partial c_i(t_2 + \tau)/\partial k_j(t_1)}{\mathrm{d}c_i(t_2)/\mathrm{d}t} + Q. \tag{34}$$

The correction term Q may be negligible in some practical calculations [123,124]. This correction term tends to zero as $(t_2 - t_1) \to \infty$, 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 *pointwise 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

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

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

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

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: $\partial^2 \boldsymbol{c}/\partial t^2 = \mathbf{J}\boldsymbol{f}(\boldsymbol{c})$.

The second approach – called *force-fit feature sensitivity analysis* [128] – is based on fitting by a least-squares procedure the concentration curve $c_i(\boldsymbol{k}, t)$ to a chosen function $c_i(\boldsymbol{\beta}, t)$ (where $\boldsymbol{\beta}$ 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 $\partial \boldsymbol{c}(\boldsymbol{\beta}, t)/\partial\boldsymbol{\beta}$ and $\partial \boldsymbol{c}(\boldsymbol{k}, t)/\partial\boldsymbol{k}$. 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 $c_i(\boldsymbol{\beta}, t)$, 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

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

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:

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

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

$$\mathbf{S}(t_2, t_1) = \int_{t_1}^{t_2} \mathbf{D}(t_2, t')\mathrm{d}t'. \tag{39}$$

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**:

$$\mathbf{F}(t_2) = \lim_{t_1 \to t_2} \mathbf{D}(t_2, t_1). \tag{40}$$

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 para-meter 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:

$$\partial c_i/\partial t = \nabla \boldsymbol{u}(\boldsymbol{x}, t)c_i + \nabla \mathbf{D}_i(\boldsymbol{x}, t)\nabla c_i + \boldsymbol{f}(\boldsymbol{c}, \boldsymbol{k}(\boldsymbol{x}, t)) + S_i(\boldsymbol{x}, t) \qquad i = 1, \ldots, n, \tag{41}$$

with initial and boundary conditions:

$$c_i(0, \boldsymbol{x}) = c_i^0(\boldsymbol{x}), \tag{42}$$

$$A_i^1(\boldsymbol{x}, t)\nabla c_i + A_i^2(\boldsymbol{x}, t)c_i = A_i^3(\boldsymbol{x}, t), \tag{43}$$

where the $\boldsymbol{x}$ space coordinate vector is an element of the space domain $\mathcal{D}$, $\boldsymbol{u}(\boldsymbol{x}, t)$ is the advection speed field, $\mathbf{D}_i(\boldsymbol{x}, t)$ is the matrix of physical or turbulent diffusion, $\boldsymbol{f}(\boldsymbol{c}, \boldsymbol{k}(\boldsymbol{x}, t))$ 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 $S_i(\boldsymbol{x}, t)$ 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:

$$\partial c_i/\partial t = \nabla \mathbf{D}_i(\boldsymbol{x},t)\nabla c_i + \boldsymbol{f}(\boldsymbol{c},\boldsymbol{k}(\boldsymbol{x},t)) \qquad i = 1,\ldots,n, \tag{44}$$

$$c_i(0,\boldsymbol{x}) = c_i^0(\boldsymbol{x}), \tag{45}$$

$$A_i^1(\boldsymbol{x},t)\nabla c_i + A_i^2(\boldsymbol{x},t)c_i = A_i^3(\boldsymbol{x},t). \tag{46}$$

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

$$\mathbf{D}(\boldsymbol{x}_2,t_2,\boldsymbol{x}',t') = \{\delta c_i(\boldsymbol{x}_2,t_2)/\delta k_j(\boldsymbol{x}',t')\}. \tag{47}$$

It is a response function which gives the linear response of the concentration of species i at $(\boldsymbol{x}_2, t_2)$ to a small variation in the parameter k_j at $(\boldsymbol{x}', t')$. The change in the concentration $c_i(\boldsymbol{x}, t_2)$ due to a small variation of $\boldsymbol{k} \rightarrow \boldsymbol{k} + \delta\boldsymbol{k}$ in the parameters is:

$$\delta\boldsymbol{c}(\boldsymbol{x},t_2) = \int_{t_1}^{t_2}\int_{\mathcal{D}} \mathbf{D}(\boldsymbol{x}',t',\boldsymbol{x},t_2)\delta\boldsymbol{k}(\boldsymbol{x}',t')\mathrm{d}\boldsymbol{x}'\mathrm{d}t'. \tag{48}$$

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):

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

This measure gives the linear response of the concentration of species i at $(\boldsymbol{x}, t)$ if the concentration of species j is perturbed by $\delta_{ij}\,\delta(t-t')\,\delta(\boldsymbol{x}-\boldsymbol{x}')$ at $(\boldsymbol{x}', t')$. 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:

$$\mathrm{d}\rho/\mathrm{d}t = f(\rho, k) + \mathbf{P}\xi^{\mathrm{T}}; \qquad \rho(0) = \rho^0, \tag{50}$$

where ρ is the stochastic vector of concentrations, ξ is a delta correlated Gaussian stochastic variable vector (white noise), and the matrix $\mathbf{P}$ 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 $p_n(c_1, t_1; \ldots; c_n, t_n)$. 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 $\boldsymbol{c}$ and the (deterministic) initial concentration sensitivity matrix $\mathbf{K}$. 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 $\boldsymbol{j}$ and $\boldsymbol{h}$ instead of rate coefficients. The components of the parameter vector $\boldsymbol{j}$ represent the weights assigned to elementary flows in the reaction network, while the parameter vector $\boldsymbol{h}$ 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 $\partial \boldsymbol{c}/\partial \boldsymbol{j}$ and $\partial \boldsymbol{c}/\partial \boldsymbol{h}$ 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*, $\mathrm{E} = \{\partial k_j / \partial c_i^{\mathrm{e}}\}$ show how the estimated parameters change when the experimentally measured concentrations $\boldsymbol{c}^{\mathrm{e}}$ 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

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

where n_e is the number of experimental data and c_i is the ith calculated concentration corresponding to the ith 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:

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

where m' is the number of estimated parameters,

$$\begin{aligned} M_{jl} = \sum_{i=1}^{n_e} \{ & (\partial^2 \ln c_i / \partial \ln k_j \, \partial \ln k_l)(c_i / c_i^{\mathrm{e}})(1 - c_i / c_i^{\mathrm{e}}) \\ & + (1 - 2c_i / c_i^{\mathrm{e}})(c_i / c_i^{\mathrm{e}})(\partial \ln c_i / \partial \ln k_j)(\partial \ln c_i / \partial \ln k_l) \end{aligned} \tag{53}$$

and

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

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 $\tilde{\mathbf{S}}$ are dimensionless and therefore their values are independent of the dimensions of the original kinetic model:

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

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,

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

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

or

$$e_3 = \int_{t_1}^{t_2} \sum_{i=1}^{n'} [(c_i^* - c_i)/c_i]^2 \mathrm{d}t.$$

Using these functions, all the species taken into account in the summation have equal weights. The sensitivity of the objective function can be calculated either directly [67,68], or from the concentration sensitivity coefficients as, for instance:

$$\partial e_1 / \partial \ln k_j = \sum_{i=1}^{n'} |\partial \ln c_i / \partial \ln k_j|, \tag{56}$$

$$\partial e_2 / \partial \ln k_j = \sum_{i=1}^{n'} (\partial \ln c_i / \partial \ln k_j)^2, \tag{57}$$

$$\partial e_3 / \partial \ln k_j = \sum_{h=2}^{l} \sum_{i=1}^{n'} (\partial \ln c_i(t_h) / \partial \ln k_j(t_1))^2, \tag{58}$$

where the effect of the change of parameter j is studied on n' species and in the latter equation, integration is replaced by summation. The sum of the squares of the normalized sensitivities is termed the *overall sensitivity* [53] and it is closely connected with the objective function of the least-squares method.

When the importance of parameters is treated, it may be worthwhile to distinguish two kinds of importance. The kind of parameter importance discussed so far may be called *tuning importance*. Tuning importances give a picture about the effectiveness of parameter changes around their nominal values for the inspected measure (concentration, objective function). If a parameter has small tuning importance with respect to the important species or features, this parameter may not necessarily be eliminated. This striking fact has been indicated several times (e.g. [2,53]). The *reduction importance* of a parameter can be determined by setting the parameter to zero and rerunning the model. The rank order of reduction importances obtained may be quite different from that of tuning importances. Sensitivity methods (except WASP) give direct information only for tuning importances.

Does this mean that there is no way in which to identify redundant reactions on the basis of sensitivity analysis? Of course not. *A reaction can be eliminated if the sensitivity of all species to the corresponding rate coefficients at any time point in the considered interval is small* [77]. An equivalent statement is that a parameter is eliminable if the norm of the corresponding column of the sensitivity matrix is small. This norm may be a maximum norm:

$$a_j' = \max_i |\partial \ln c_i / \partial \ln k_j|, \tag{59}$$

or a Euclidean norm:

$$d_j' = \left(\sum_{i=1}^{n} (\partial \ln c_i / \partial \ln k_j)^2 \right)^{1/2} . \tag{60}$$

Note that the overall sensitivities (when all species are considered) are the squares of the Euclidean norm and therefore they give the same estimated rank order of reduction importances.

So far, only the concentration sensitivities have been mentioned and the question of feature sensitivities has not been discussed. In general, the jth feature sensitivity coefficient refers only to the tuning importance of the jth parameter considering the specific feature and it must not serve as a basis for mechanism reduction [2]. If this feature is closely connected to all the necessary species (see section 4.2), this value might refer also to reduction importance. Such a dominant feature sensitivity might be the period sensitivity of an oscillating reaction [121].

Having discussed what the importance of parameters means, one may ask *when* is a parameter important. All the sensitivity matrices discussed in the preceding sections (except matrix **F** and the quasi-stationary sensitivities) belong to a time interval which is determined by the time of perturbation t_1 and the time of observation t_2 [1,120]. Both the tuning and the reduction importances deduced from such matrices belong to the time interval $[t_1, t_2]$.

Reduction importances belonging to a definite reaction time can be obtained by the study of the algebraic rate sensitivity matrix $\tilde{\mathbf{F}}$. This matrix can be processed like other sensitivity matrices [120]. If only column i of the matrix $\tilde{\mathbf{F}}$ is considered, reactions having the greatest effect on the rate of production of species i at a given reaction time are identified. Similarly to the case of concentration sensitivities, the effect of parameters on the rate of a group of species can be inspected. If all species are taken into account, the reduction importances at a given time are obtained. If a reaction proves to be important at least at a single time point in an interval, this reaction must not be eliminated from the mechanism. The investigation of the change of reduction importances as the reaction proceeds can reveal fine details of the operation of the mechanism.

Hitherto, the importance of individual parameters in a reaction was discussed. In reality, groups of joint parameters influence the concentrations. These parameter groups cause functional connections between the sensitivity coefficients and they can be identified by the mere inspection and comparison of the elements of the normalized local concentration sensitivity matrix [77,66,38,1]. In the next section, a more convenient way is presented for the identification of these parameter groups.

4.1.1. Principal component analysis

Let us use the objective function e_3 to assess the effect of parameters on a group of species. Replacing the integral with summation and introducing the normalized parameters $\alpha_j = \ln k_j$ ($j = 1, \ldots, m$), the function e_3 is approximated by:

$$e_3(\alpha) \approx \sum_{h=2}^{l} \sum_{i=1}^{n'} [(c_i^*(t_h) - c_i(t_h))/c_i(t_h)]^2. \tag{61}$$

This objective function can also be given [53] by

$$e_3(\alpha) \approx (\Delta\alpha)^{\mathrm{T}} \tilde{\mathrm{S}}^{\mathrm{T}} \tilde{\mathrm{S}}(\Delta\alpha), \tag{62}$$

where $\Delta\alpha = \alpha - \alpha^0$ and the matrix $\tilde{\mathrm{S}}$ is defined as

$$\tilde{\mathrm{S}} = \begin{bmatrix} \tilde{\mathrm{S}}_2 \\ \tilde{\mathrm{S}}_3 \\ \vdots \\ \tilde{\mathrm{S}}_h \\ \vdots \\ \tilde{\mathrm{S}}_l \end{bmatrix}, \tag{63}$$

where an element of matrix $\tilde{\mathrm{S}}_h$ is $\partial \ln c_i(t_h)/\partial \ln k_j(t_1)$.

Let U denote the matrix of normalized eigenvectors U_j of $\tilde{\mathrm{S}}^{\mathrm{T}}\tilde{\mathrm{S}}$ such that $U_j^{\mathrm{T}} U_j = 1, j = 1, \ldots, m$. Then the new set of parameters

$$\psi = \mathrm{U}^{\mathrm{T}}\alpha, \tag{64}$$

called *principal components*, leads to the canonical form of the objective function e_3:

$$e_3 \approx \sum_{j=1}^{m} \lambda_i (\Delta\psi_i)^2, \tag{65}$$

where $\Delta\psi = \mathrm{U}^{\mathrm{T}}\Delta\alpha$ and $\lambda_1 \geq \lambda_2 \geq \ldots \geq \lambda_m$ are the eigenvalues of $\tilde{\mathrm{S}}^{\mathrm{T}}\tilde{\mathrm{S}}$. It is apparent from eqs. (64) and (65) that the eigenvectors of matrix $\tilde{\mathrm{S}}^{\mathrm{T}}\tilde{\mathrm{S}}$ reveal the related parameters and the corresponding eigenvalues express the weight of these parameter groups [53].

Principal component analysis should be preferred to other methods which describe the effect of individual parameters on a group of species concentrations. When tuning importances are investigated, the method can identify those cases where, for instance, only the ratio or the product of two parameters influences the objective function. Moreover, principal component analysis can be very useful in mechanism reduction. Sometimes, the elimination of the reactions one by one may cause significant changes in the solution, while elimination of reaction pairs has no significant consequences [53,122]. Principal component analysis can be used to identify groups of reactions which can be eliminated.

Although the principal component analysis technique was suggested originally for the analysis of local concentration sensitivity matrices, it can be adapted to the study of other sensitivity matrices, too. The use of principal component analysis for the investigation of the rate sensitivity matrix **F** is discussed in [120]. Applications of principal component analysis are found in refs. [53,54,61,91,120–122,164,166,168].

4.1.2. Derived sensitivities

While principal component analysis provides information about both the importance and the connection of parameters, calculation of *derived sensitivities* might give a deeper insight into the interconnection of parameters.

The change of a concentration vector at t_2 as a result of the change of a parameter vector at t_1 can be expressed by utilizing the normalized sensitivity matrix $\tilde{\mathbf{S}}$:

$$\mathrm{d}\ln \boldsymbol{c}(t_2) = \tilde{\mathbf{S}}\,\mathrm{d}\ln \boldsymbol{k}(t_1). \tag{66}$$

Let us rewrite this equation into the following form:

$$\begin{pmatrix}\mathrm{d}\ln \boldsymbol{c}'(t_2)\\ \mathrm{d}\ln \boldsymbol{c}''(t_2)\end{pmatrix} = \left(\begin{array}{c|c}\tilde{\mathbf{S}}_1 & \tilde{\mathbf{S}}_2\\ \hline \tilde{\mathbf{S}}_3 & \tilde{\mathbf{S}}_4\end{array}\right)\begin{pmatrix}\mathrm{d}\ln \boldsymbol{k}'(t_1)\\ \mathrm{d}\ln \boldsymbol{k}''(t_1)\end{pmatrix}. \tag{67}$$

Interchanging variable vectors $\ln \boldsymbol{c}'$ and $\ln \boldsymbol{k}'$ leads to

$$\begin{pmatrix}\mathrm{d}\ln \boldsymbol{k}'(t_1)\\ \mathrm{d}\ln \boldsymbol{c}''(t_2)\end{pmatrix} = \left(\begin{array}{c|c}\tilde{\mathbf{D}}_1 & \tilde{\mathbf{D}}_2\\ \hline \tilde{\mathbf{D}}_3 & \tilde{\mathbf{D}}_4\end{array}\right)\begin{pmatrix}\mathrm{d}\ln \boldsymbol{c}'(t_2)\\ \mathrm{d}\ln \boldsymbol{k}''(t_1)\end{pmatrix}. \tag{68}$$

In eq. (68), $\ln \boldsymbol{c}'$ and $\ln \boldsymbol{k}''$ are independent variables, while $\ln \boldsymbol{k}'$ and $\ln \boldsymbol{c}''$ are dependent variables. Using the rules of multivariable calculus, the blocks of matrix **D** can be obtained by

$$\begin{aligned}\tilde{\mathbf{D}}_1 &= \tilde{\mathbf{S}}_1^{-1},\\ \tilde{\mathbf{D}}_2 &= -\tilde{\mathbf{D}}_1\tilde{\mathbf{S}}_2,\\ \tilde{\mathbf{D}}_3 &= \tilde{\mathbf{S}}_3\tilde{\mathbf{D}}_1,\\ \tilde{\mathbf{D}}_4 &= \tilde{\mathbf{S}}_4-\tilde{\mathbf{S}}_3\tilde{\mathbf{D}}_1\tilde{\mathbf{S}}_2.\end{aligned} \tag{69}$$

If matrix $\tilde{\mathbf{S}}_1$ is not a square matrix, a least-squares solution is recommended to obtain matrix $\tilde{\mathbf{D}}_1$ [145]. The blocks of the first-order normalized derived sensitivity matrix $\tilde{\mathbf{D}}$ have the following elements:

$$\begin{pmatrix} \tilde{\mathbf{D}}_1 & \tilde{\mathbf{D}}_2 \\ \tilde{\mathbf{D}}_3 & \tilde{\mathbf{D}}_4 \end{pmatrix} = \left(\begin{array}{c|c} \dfrac{\partial \ln \boldsymbol{k}'(t_1)}{\partial \ln \boldsymbol{c}'(t_2)} & \dfrac{\partial \ln \boldsymbol{k}'(t_1)}{\partial \ln \boldsymbol{k}''(t_1)} \\ \hline \dfrac{\partial \ln \boldsymbol{c}''(t_2)}{\partial \ln \boldsymbol{c}'(t_2)} & \dfrac{\partial \ln \boldsymbol{c}''(t_2)}{\partial \ln \boldsymbol{k}''(t_1)} \end{array} \right). \tag{70}$$

All these derived sensitivity coefficients have an unusual interpretation, as discussed below.

(1) *Matrix* $\tilde{\mathbf{D}}_1$: *Parameter–observation interdependence*

The coefficients of matrix $\tilde{\mathbf{D}}_1$ provide information on the accuracy of the determination of parameters $\boldsymbol{k}'$ if concentrations $\boldsymbol{c}'$ are monitored. In an experiment, it is desirable to choose the experimental conditions in such a way as to minimize $\partial \ln k_j'/\partial \ln c_i'$. This ensures that the uncertainty in the monitored species concentration c_i is not magnified in the estimation of the rate constant k_j.

(2) *Matrix* $\tilde{\mathbf{D}}_2$: *Parameter–parameter interdependence*

If the value of k_j is changed at t_1, the derivative $\partial \ln k_i/\partial \ln k_j$ indicates the direction and magnitude of the necessary change in the rate constant k_i at t_1 which reproduces the original concentration vector $\boldsymbol{c}'$ at t_2.

(3) *Matrix* $\tilde{\mathbf{D}}_3$: *Interdependence of different observations*

Let us suppose that in an experiment the concentration profiles for some species are monitored, but that this information is inadequate to identify the mechanism and therefore the concentrations of further species have to be monitored. The less the connection between the old and new observations regarding the parameters $\boldsymbol{k}'$ to be determined, the greater the information increase. The task is to scan the observation–observation sensitivities in order to find those observables which are the least dependent on the already measured concentrations.

(4) *Matrix* $\tilde{\mathbf{D}}_4$: *Observation–parameter interdependence*

One has to realize that the coefficients of matrix $\tilde{\mathbf{D}}_4$ are different from the elementary sensitivity coefficients $\partial \ln c_i/\partial \ln k_j$, since in the former case concentrations $\boldsymbol{c}'$ are held fixed. Applications of these derived sensitivities have not been reported so far.

Derived sensitivity coefficients were introduced by Dougherty et al. [43], although the matrix $\tilde{\mathbf{D}}_1$ has been calculated in ref. [131], too. Larter et al. showed that derived sensitivities can be computed directly, that is, without *a priori* evaluation of elementary sensitivities [139]. Yetter et al. calculated second-order derived sensitivities [74] as well, and Demiralp and Rabitz presented derived sensitivity densities [138]. Recently, Yetter et al. [74] demonstrated the interpretation of derived local sensitivity coefficients on the example of a large reaction mechanism. Derived sensitivities were also applied in the investigation of flames [55].

Since partitioning of matrix $\tilde{\mathbf{S}}$ in eq. (66) is arbitrary, a number of different derived sensitivities are possible which may be calculated from the same matrix $\tilde{\mathbf{S}}$. Therefore, it is not practical to search for parameter dependence in this way. However, the existence of assumed connections can be proved or refuted by appropriately calculated derived sensitivities.

Another type of derived sensitivities can be calculated from normalized experimental sensitivities and from the normalized local concentration sensitivities using the chain rule [145]:

$$\partial \ln c_i / \partial \ln c_j^{\mathrm{e}} = \sum_{l=1}^{m'} (\partial \ln c_i / \partial \ln k_l)(\partial \ln k_l / \partial \ln c_j^{\mathrm{e}}). \tag{71}$$

These coefficients interrelate the calculated and the experimentally measured concentrations.

4.2. IMPORTANCE AND INTERCONNECTION OF VARIABLES

The aim of most kinetic modeling studies is to properly describe the concentration changes of some species considered to be important and/or to reproduce some kinetic features of the reaction. A reaction mechanism has to contain both the reactions of these *important species* and the reactions of those species which are *necessary* to accurately calculate the concentration changes of the important species. In a large reaction mechanism, some species may be *redundant* and their concentration need not be calculated. Note that the products of important reactions may be redundant species.

The decision about which species and/or features are considered important depends on the objective of the modeling. Here, two methods [122] are given for the identification of redundant species. Both methods are based on the fact that necessary species are strongly connected to important species and features.

4.2.1. Identification of redundant species via reduced models

According to this method, a species is redundant if the elimination of its consuming reactions does not cause significant deviations from the solution of the full model with respect to the concentration of important species and/or important features. Some redundant species are formed in fast reversible reactions and they cannot be identified by the above test. Therefore, each species has to be reinvestigated by the simultaneous elimination of its fast forming and consuming reactions; if the solution of the reduced model is practically identical to the solution of the full model considering important species and/or features, the investigated species is redundant as well.

4.2.2. Identification of redundant species via the investigation of the Jacobian

A species is redundant if its concentration change has no significant effect on the production rate of the important species. Such an effect is indicated by an element of the normed Jacobian $\partial \ln f_i / \partial \ln c_j$. The influence of the change of the concentration of species i on the rate of production of an N-member group of important species can be taken into account by an overall sensitivity-type measure:

$$B_i = \sum_{n=1}^{N} (\partial \ln f_n / \partial \ln c_i)^2. \tag{72}$$

This measure quantifies only the direct effects. Indirect links can be revealed by an iteration procedure. The important species, together with the best-ranked species by the merit of their B_i values, are taken into account in the summation in eq. (72) to identify new necessary species. This procedure is repeated until convergence. Redundant species are those which do not take place in the summation at the end.

The second method is less effective, since redundant species formed in fast reversible reactions cannot be identified and the effect on important features cannot be investigated. However, this method is suitable for studying how the categories of necessary and redundant species change as the reaction proceeds.

4.3. SEPARATION OF THE SECULAR TERM

When oscillating reactions are studied by sensitivity analysis, one has to face problems which are unknown in the investigation of other reactions. The change of a parameter or an initial concentration causes a phase shift in the concentration waves [82,125]. Moreover, a parameter perturbation in the general case changes not only the wave form, but also the period time of the oscillator. The consequence of a change of the period time is that the nominal and the perturbed solutions move away from each other as the time proceeds. Therefore, the calculated local concentration sensitivities grow without bound in the limit of large times and they consist of two terms: The first one (called *structural sensitivity*) is a periodic function which carries information about the change of the form of the concentration wave. The second, the so-called *secular term*, is proportional to $t = t_2 - t_1$ and it becomes arbitrarily large as t becomes large.

An important step in the interpretation of the sensitivity coefficients of oscillators is to reveal the information inherent in structural sensitivities by the separation of the secular term. Two ways were proposed for the separation of the secular term. According to the first [80], the phase lead or lag between the original and perturbed solutions is calculated by a linear approach from the period sensitivity. Thus, the phase lead or lag at time t_2 is approached by $(t/\tau)(\partial\tau/\partial k_j)$, where τ is the period time and $t = t_2 - t_1$. The corresponding equation for the separation of the secular term is:

$$\frac{\partial c_i(t_2)}{\partial k_j(t_1)} = \left(\frac{\partial c_i(t_2)}{\partial k_j(t_1)}\right)_\tau - \frac{t}{\tau}\frac{\partial\tau}{\partial k_j}\frac{\mathrm{d}c(t_2)}{\mathrm{d}t}. \tag{73}$$

Once the period sensitivities $\partial\tau/\partial k_j$ have been calculated by eq. (34), the structural sensitivities $(\partial c_i/\partial k_j)_\tau$ are derived by a simple addition.

Larter [126] also presented a more involved, but more general, way for the separation of the secular term, based on a Floquet theoretic approach. This method is also applicable to unstable oscillators.

The second way [125] takes into account the actual phase lead or lag $(\partial t/\partial k_j)_\Phi$ at time t instead of the linear approach. The corresponding equation is:

$$\frac{\partial c_i(t_2)}{\partial k_j(t_1)} = \left(\frac{\partial c_i(t_2)}{\partial k_j(t_1)}\right)_\Phi - \left(\frac{\partial t}{\partial k_j}\right)_\Phi \frac{\mathrm{d}c_i(t_2)}{\mathrm{d}t}, \tag{74}$$

where $(\partial c_i/\partial k_j)_\Phi$ and $(\partial t/\partial k_j)_\Phi$ are called *path-independent sensitivity* and *phase sensitivity*, respectively. The calculation of phase sensitivities is more complicated than the calculation of $\partial\tau/\partial k_j$, but path-independent sensitivities can be considered the exact structural sensitivity coefficients. Kramer et al. [125] also elaborated equations for the calculation of second-order period, structural, path-independent, and phase sensitivities.

Recently, the concept of the secular term was also applied to non-oscillatory systems [76]. The secular term of a general sensitivity coefficient corresponds to the change in the time scale of the reaction caused by the change of a parameter. The secular term free sensitivity coefficients were applied to the prediction of the model solution for parameter values away from the nominal parameter values.

Short summaries dealing with the handling of the problem of the secular term based on eq. (73) are found in refs. [146] and [147]. The separation of the secular term has been illustrated so far only in the case of small model systems, such as Brusselator [82,126], the Lotka–Volterra model [80], and other simple systems [76,125].

5. Software

Computer programs make sensitivity tools applicable for the chemist. All methods discussed so far are reproducible from their announcing articles, but coding a sophisticated method might be an exhausting task. There are a number of articles in which the authors report on their efforts for coding a method, and they give tips on how to construct an efficient program. Such articles are refs. [102] and [103] for the FAST method, ref. [69] for the Green function method (version (1)), and ref. [65] for the SGFM/II method.

Unfortunately, only few articles exist in which a ready computer code is published. FORTRAN codes are presented in [89] for the polynomial approximation method and in [51] for the decomposed direct method.

Several programs are offered in the literature for sensitivity calculations. A computational implementation of the GFM/AIM method is available from the authors of ref. [148]. Moreover, this software was also combined with the CHEMKIN chemical kinetics software [149], yielding a production code called CHEMSEN [150] to model isothermal constant-volume chemical kinetics systems. This program was reproduced by Hayashi and Fujiwara [15]. Caracotsios and Steward offer a program package named DASAC [50] which is based on an improved direct method. The combination of this program with the CHEMKIN package is called SENKIN [151] and is applicable for the sensitivity study of a homogeneous reacting gas mixture in a closed system. Another realization of the decoupled direct method is offered under the name ODESSA [48].

The author of this review also offers a program package, named KINAL [152], which is written for the ***kin***etic ***anal***ysis of complex reaction mechanisms. The package includes programs for the integration of kinetic differential equations, for the construction of the rate sensitivity and quasi-stationary sensitivity matrices, and for the calculation of the local concentration sensitivity matrix based on the decomposed direct method. The principal component analysis is applied to reveal information inherent in these matrices.

6. Applications

Applications of sensitivity analysis cover very important areas of kinetic modeling. Usually, several sensitivity tools can be used to solve the same problem and the selection of the appropriate method is based on a trade-off between accuracy and computer time demand. Most problems may also be solved by methods other than sensitivity analysis, but they will not be discussed here.

6.1. UNCERTAINTY ANALYSIS AND PARAMETRIC SCALING

All parameters of mathematical models have more or less uncertainty. *Uncertainty analysis* methods are addressed to calculate the uncertainty of model results caused by the uncertainties of the parameters. The uncertainty of a model output may be so significant that the practical value of the model may be questioned.

In sensitivity analysis, each parameter is perturbed to the same extent, while in uncertainty analysis (also called sensitivity/uncertainty analysis), the real uncertainty associated with each parameter is taken into account. Such uncertainty information is derived from the statistical analysis of experimental data. Laboratory controllable parameters (e.g. the temperature of a thermostat) also have an uncertainty, caused by the experimental apparatus.

Global methods are directly applicable to uncertainty analysis. Such calculations have been performed by the Monte Carlo method [115–117], by the Latin hypercube method [36,118], and by the FAST method [107,108].

Local sensitivity information can also be a basis for uncertainty analysis. The mean value and variance of the concentration c_i can be determined [46] by the equations:

$$\langle c_i \rangle = c_i + \tfrac{1}{2} \sum_{j=1}^{m} (\partial^2 c_i / \partial k_j^2) \sigma^2(k_j) + \sum_{j=1}^{m} \sum_{l=j+1}^{m} (\partial^2 c_i / \partial k_j \, \partial k_l) \operatorname{cov}(k_j, k_l); \quad (75)$$

$$\sigma^2(c_i) = \sum_{j=1}^{m} (\partial c_i / \partial k_j)^2 \sigma^2(k_j) + 2 \sum_{j=1}^{m} \sum_{l=j+1}^{m} (\partial c_i / \partial k_j)(\partial c_i / \partial k_l) \operatorname{cov}(k_j, k_l)$$
$$+ \sum_{j=1}^{m} (\partial c_i / \partial k_j)(\partial^2 c_i / \partial k_j^2) \mu_3(k_j), \quad (76)$$

where μ_3 is the third central moment. Frequently, only the mean value and the variance of parameters are known, and in such cases the last term in eq. (75) and the two second terms of eq. (76) can be neglected. However, knowledge of the covariance matrix is essential if the parameters are highly correlated.

The use of linear sensitivity information in uncertainty analysis requires orders of magnitude less computational effort, but the results obtained may be misleading if the uncertainty of the parameters is large. Non-global uncertainty analyses were also carried out by Dodge and Hecht [25] and by Butler [153]. Their considerations were based on sensitivities calculated by the brute force method.

While uncertainty analysis investigates the influence of parameters on the solutions from a stochastic point of view, this problem has a deterministic equivalent: What will be the new solution of the model at time t_2 if the parameters are changed at time t_1? The process of extrapolation of a modeling result to new parametric conditions is called *parametric scaling*.

The simplest solution of the problem of parametric scaling is based on the application of the Taylor series, in which the coefficients are the local first- and higher-order sensitivity matrices (cf. eqs. (2) and (3)). As an example, Taylor series approximations were used [125] to predict the new amplitude and period time of a limit cycle oscillator when the parameters are changed significantly.

In chemical kinetics, the exponential behaviour of species concentrations is ubiquitous and therefore eq. (77) gives a better approximation in most cases than the first-order Taylor series [43]:

$$c_i(\boldsymbol{k} + \Delta \boldsymbol{k}) \cong c_1 \exp\left[\sum_{j=1}^{m} (\Delta k_j / c_i)(\partial c_i / \partial k_j) \right]. \quad (77)$$

Hwang [40] applied a similar equation supplemented by second-order terms, and found it much better than eq. (77).

Kramer et al. [76] examined several strategies for parametric scaling. They showed that the previous methods may provide physically unrealistic results when $\boldsymbol{c}$ has known bounds. First- and higher-order alternative equations are proposed with built-in constraints, thus expanding the parametric region in which the extrapolation may be valid. They also demonstrated that secular term free sensitivities can be better applied for parametric scaling, both in the case of oscillatory and in the case of non-oscillatory systems.

6.2. PARAMETER ESTIMATION

A usual task in chemical kinetics is the fitting of model parameters to experimental data. Suppose that the structure of the regression model allows an adequate fit. Then the greatest possible pitfall in a parameter estimation procedure is to encounter an ill-conditioned problem. Here, we present a procedure [53], based on the eigenvector–eigenvalue decomposition of matrix $\tilde{\mathbf{P}}$, to avoid such problems. The definition of this matrix is

$$\tilde{\mathbf{P}} = \sum_{l=1}^{L} \tilde{\mathbf{R}}^{\mathrm{T}}(t_l)\mathbf{W}_l\tilde{\mathbf{R}}(t_l), \tag{78}$$

where matrix $\tilde{\mathbf{R}} = (\partial \ln \boldsymbol{h}/\partial \ln \boldsymbol{c})(\partial \ln \boldsymbol{c}/\partial \ln \boldsymbol{k})$, the function $\boldsymbol{h}(\boldsymbol{c})$ is the instrumental function, i.e. the function which converts the calculated concentrations into calculated signals of the experimental apparatus, and L is the number of measurements. The matrix $\mathbf{W}_l$ is the weighting matrix belonging to the lth data set, which may be identical to the unit matrix (unweighted parameter estimation) or is chosen as the inverse of the covariance matrix.

Parameters which are not related to large eigenvector elements of large eigenvalues cannot be determined by parameter estimation. The values of these parameters have to be fixed to avoid singularity. In addition, very often only the value of the quotient (or product) of some parameters can be determined. This situation is indicated by a low-eigenvalued normed eigenvector which has a form similar to $(0.707, \pm 0.707, 0, \ldots, 0)$. In this case, one of the coupled parameters has to be fixed. However, one has to keep in mind that the ratio of the parameters and not their real values are determined! This procedure is also a solution for the problem of the deep-valley-shaped objective functions, which occur often in chemical kinetic modeling [2].

The matrix $\tilde{\mathbf{P}}$ depends on the values of parameters. Since the exact values of parameters are not known, one has to calculate the matrix using estimated parameters. It is advisable to carry out the eigenvalue–eigenvector decomposition of the recalculated matrix $\tilde{\mathbf{P}}$ in each cycle of parameter estimation. The list of fixed parameters may have to be revised as the parameter set becomes more and more accurate.

Note that the principal component analysis of matrix $\tilde{\mathbf{S}}^{\mathrm{T}}\tilde{\mathbf{S}}$ is obtained when the concentrations are measured directly ($\boldsymbol{h} = \boldsymbol{c}$) and weights are not used ($\mathbf{W} = \mathbf{I}$).

Having determined which parameters have to be fixed, one can start the parameter estimation procedure. The Marquardt algorithm has proved to be the most effective tool for parameter estimation in chemical kinetics [154]. According to this method, the parameters are fitted by an iteration and the new parameter set is determined using the following equation:

$$\boldsymbol{\beta}^{(i+1)} = 1 + (\tilde{\mathbf{P}}^{\mathrm{T}}\tilde{\mathbf{P}} + \lambda \mathbf{I})^{-1}\tilde{\mathbf{P}}^{\mathrm{T}} \sum_{l=1}^{L} \tilde{\mathbf{R}}^{\mathrm{T}}(t_l)\mathbf{W}_l[\boldsymbol{y}_l - \boldsymbol{h}(\boldsymbol{c}(t_l))], \tag{79}$$

where an element of vector $\boldsymbol{\beta}^{(i+1)}$ is the ratio of the new and of the old estimated value of parameter j, i.e. $\beta_j^{(i+1)} = k_j^{(i+1)}/k_j^{(i)}$, $\boldsymbol{y}_l$ is the vector of measured data in the lth experiment, and λ is the Marquardt parameter. All vectors and matrices on the right-hand side of eq. (79) are evaluated using the parameter vector $\boldsymbol{k}^{(i)}$.

Efficient numerical methods, developed for the calculation of local concentration sensitivities, are well applicable in a parameter estimation. The sensitivity matrices have to be computed using the first-guess values of parameters. Then matrices $\tilde{\mathbf{R}}$ and $\tilde{\mathbf{P}}$ are calculated, the parameters to be fixed are selected, a new parameter set is obtained by eq. (79), and the procedure is repeated until convergence is achieved.

Above, it was assumed that the structure of the regression model is adequate for fitting the data. If not, a discrepancy between the measured and calculated data will remain even in the case of the best fit. In this case, new parameters (new reactions) have to be searched for to complement the original model. The values of the assumed new parameters are set to zero and a sensitivity analysis is carried out. The solution of the model remains unchanged, but great sensitivity indicates that these parameters might effectively change the solution. Such calculations were described in refs. [71] and [79]. Note, however, that the effect of a new parameter may be very different if its value is different from zero.

6.3. DESIGN OF EXPERIMENTS

Each laboratory experiment should be preceded by experimental design to ensure the maximal effectiveness of laboratory work. The problem of experimental design can be interpreted both from strategical and tactical approaches.

If one has a large multi-parameter model to improve, one has to identify those parameters which should be known more precisely. These parameters are not necessarily the most uncertain parameters, but they are those parameters which cause the greatest uncertainty in the modeling results. Therefore, the parameters to be investigated experimentally have to be selected on the basis of the result of an uncertainty analysis.

The next step is the design of an experiment in which more accurate values for the critical parameters are determined. There are several ways of performing experiments: often one can select the species' concentrations to be measured, the time points of the measurement, and the initial concentrations of reactants. On the basis of a simulated experiment, matrix $\tilde{\mathbf{P}}$ has to be calculated according to eq. (78). The principal component analysis of matrix $\tilde{\mathbf{P}}$ reveals if the value of the parameter in question can be determined. The matrix $\tilde{\mathbf{P}}$ has to be recalculated for different planned reaction circumstances until the parameter to be determined is a single dominant element of a principal component of large eigenvalue.

The above described "tactical experimental design" can also be carried out by using either derived sensitivities or experimental sensitivities. The appropriate elements of the derived sensitivity matrix $\tilde{\mathbf{D}}_1$ have to be minimized to decrease the variance of parameters to be determined. The matrix $\tilde{\mathbf{D}}_2$ gives information about the influence of the value of fixed parameters on the value of fitted parameters. The selection of new concentrations to be measured besides the already measured ones can be based either on matrix $\tilde{\mathbf{D}}_3$ or on the derived experimental sensitivity matrix. Elementary experimental sensitivities can be used to identify those parameters of the assumed model which are strongly affected by noisy data.

6.4. REPRO-MODELING

When modeling a spatially inhomogeneous chemical reaction system, the kinetic equations have to be solved at each grid point. This means several hundreds or thousands of solutions of large sets of ODEs while their initial conditions cover a physically reasonable (usually not very large) domain. After the solution of the kinetic equations, the transport equation has to be solved over the same time interval. This time interval Δt is determined by the stability and/or the accuracy of the transport equation and it is usually not very long, while stiff ODE solvers require time to "start up" and are therefore not very efficient over a short time interval. The consequence is that an overwhelming part of the computer time used in modeling a space–time system is consumed by the description of chemical reactions.

The application of initial concentration sensitivities offers a simple and efficient solution for this problem [60]. This procedure is called "repro-modeling". The domain of initial concentrations is covered by a grid of C^0 vectors. The solution of kinetic equations $F(C^0, \Delta t)$ and the first- and second-order initial concentration sensitivities

$$\left.\frac{\partial F(\Delta t)}{\partial c}\right|_{c=C^0} \quad \text{and} \quad \left.\frac{\partial^2 F(\Delta t)}{\partial c\, \partial c}\right|_{c=C^0}$$

are calculated for each C^0 initial concentration set and are stored ("parametrization of the mechanism"). Then the solution of the kinetic equations after a time interval Δt for any arbitrary c^0 initial concentrations within the domain of interest can be approximated by

$$c(c^0,\Delta t) \approx F(C^0,\Delta t)+\sum_i \left.\frac{\partial F(\Delta t)}{\partial c_i}\right|_{c=C^0}(c_i^0-C_i^0)$$
$$+\ \tfrac{1}{2}\sum_i\sum_j \left.\frac{\partial^2 F(\Delta t)}{\partial c_i\,\partial c_j}\right|_{c=C^0}(c_i^0-C_i^0)(c_j^0-C_j^0), \tag{80}$$

where C^0 is chosen to be close to c^0.

Dunker [60] applied this procedure to a photochemical mechanism for oxidant formation in urban areas. He showed that the computational effort required for the solution of the kinetic equations by this method was reduced by more than two orders of magnitude, while the approximated concentrations agreed fairly well with the exactly calculated ones even after fifteen hours simulation time.

Marsden et al. [155] also presented a similar approximation, where the whole initial concentration domain is covered by one second-order empirical polynomial. This procedure is closely related to the determination of sensitivities using approximate empirical models. In the method of Dunker, the coefficients of the second-order polynomial depend on initial concentrations, but this is not the case in the method of Marsden et al., and therefore the second way is simpler but provides less accurate solutions.

6.5. STABILITY ANALYSIS

If the solution of a mathematical model is perturbed at t_1 by $\delta c(t_1)$, the deviation between the perturbed and the nominal solutions at t_2 can be expressed by

$$\delta c(t_2) = \mathbf{K}(t_2, t_1)\, \delta c(t_1), \tag{81}$$

where **K** is the initial concentration sensitivity matrix (see eq. (10)). The growth or shrinkage of δc shows the stability of the model with respect to changes in the initial concentrations. A useful method to assess the stability is to perform an eigenanalysis of matrix **K** [82,84]. The eigenvalues of **K** indicate the stability, instability, or marginal stability of certain combinations of deviations from the initial condition in the Lyapunov sense. The eigenvectors indicate the direction of deviation from the solution in state space.

The mixed second-order sensitivity coefficients can be interpreted as the sensitivity of matrix **K**:

$$\frac{\partial^2 c(t_2)}{\partial k_l(t_1)\,\partial c^0(t_1)} = \frac{\partial \mathbf{K}(t_2,t_1)}{\partial k_l(t_1)}. \tag{82}$$

The analysis of matrix $\partial \mathbf{K}/\partial k_l$ provides the sensitivity of stability eigenvectors and eigenvalues to model parameters. This gives information on how the stability changes, both in magnitude and in direction, as a function of system parameters.

The concentration sensitivity matrix $\mathbf{S}$ can also be interpreted as a measure of the stability of the solution with respect to the change of the parameters. (The second-order sensitivities can be considered to be the sensitivity of these stability measures.) If small perturbations in the model parameters cause exorbitant changes in the model predictions, the usefulness of the model may be questioned [143]. Larter demonstrated [80] the structural instability of an oscillating reaction model by the calculation of secular term free sensitivities.

6.6. INVESTIGATION OF REACTION MECHANISMS

The study of the effect of parameter perturbance on the solution, which is the essence of dynamic sensitivity analysis, can provide significant information on the structure of reaction mechanisms. The change of a parameter belonging to reaction j causes a direct concentration change only in the case of those species which are reactants or products in this reaction. The direct concentration changes cause further changes in the concentration of other species [120]. The latter indirect (nonlinear) effects cannot be predicted by screening analysis or by studying matrix $\tilde{\mathbf{F}}$, and the *nonlinear effects* revealed by dynamic sensitivity analysis can be used to settle particular mechanistic questions [1,26,43,44,72,97,106,132]. The sensitivity information belongs to a time interval and this interval can be changed by changing the time of perturbation t_1 and the time of observation t_2. This was called "the variable-initial-time procedure" by Hwang [1].

Often, one is interested in the structure of reaction systems and the importance of reactions at a definite reaction time which corresponds to a given concentration set. Such questions can be answered by the analysis of matrix $\tilde{\mathbf{F}}$ [120]. This technique can have advantages also in the study of distributed parameter systems, since in some cases the time-consuming functional sensitivity analysis may be avoided [164].

Rate-limiting steps are exposed by very large sensitivity coefficients [104,131,156]. Recently, Ray [119] proposed the following definition of rate-limiting steps: a reaction step is rate-limiting if the increase of the rate coefficient causes a significant increase of the overall reaction rate. Therefore, the rate-limiting step can be identified by inspecting the ith row of the dynamic rate sensitivity matrix, where the rate of production of the ith species is considered to be identical to the overall rate of the reaction. A possible extension of the original definition is to assign a rate-limiting step to the formation or consumption of each species of a complex reaction. The rate-limiting step of the ith species can be identified (if it exists) by searching for a very large element in the ith row of the dynamic rate sensitivity matrix. This extension of the definition may be useful, since in the case of some complex reaction systems (e.g. smog mechanisms), the concept of an overall reaction rate is meaningless and therefore the original definition of a rate-limiting step cannot be applied.

The existence of *fast equilibrium conditions* or *quasi-stationary species* causes interactions between the parameters. They can be identified by one of the methods described in section 4.1. As an example, such parameter connections can be revealed by principal component analysis of the local concentration sensitivity [53,54] or the rate sensitivity matrices [120,168].

A list of sensitivity studies on complex reaction mechanisms is given in table 1. This table can be used as a source of citations to find which difficulties have been encountered using the sensitivity method of interest. Furthermore, in examining a reaction system, experience obtained by the investigation of similar reactions can be utilized.

6.7. REDUCTION OF REACTION MECHANISMS

The WASP method [111] is the only sensitivity method which gives direct information about the effect of the elimination of parameters from a mechanism. Unfortunately, the application of WASP for mechanism reduction requires an unreasonable amount of computer time.

There are a number of methods for the estimation of the reduction importances. Grigoryeva et al. proposed a mechanism reduction procedure based on repetitive calculations of FAST sensitivity coefficients [101]. The method of Pierce et al. [104] is also based on FAST sensitivity coefficients. Frenklach proposed a synoptic study of appropriate feature sensitivities and of reaction rates [2].

Mechanism reduction can be based on the direct investigation of local concentration sensitivity coefficients [1,77], or on vector norm analysis or principal component analysis of the local concentration sensitivity [53,54,164], rate sensitivity [120,164,166,168], or quasi-stationary sensitivity [91] matrices. Species taken into account in the analyses can be selected by one of the methods described in section 4.2. Combinations of the above procedures give an enormous number of variations. The method [122] described below seems to be effective regarding both the computer time requirements and the size of the obtained reduced mechanism.

First, the modeler has to decide which species concentrations or features of the full mechanism are required to be reproduced by the reduced mechanism. The first method described in section 4.2 provides the list of species necessary in the reduced mechanism. Then, a principal component analysis of matrix $\tilde{\mathbf{F}}$ is fulfilled with important and necessary species in the objective function of the method. This analysis has to be carried out for several reaction times allocated in the entire time interval of interest. A reaction must not be eliminated if it proves to be important at any time. The next step is to eliminate the redundant reactions from the mechanism. Finally, the success of mechanism reduction is tested by comparing the solutions of full and reduced mechanisms.

The reduced mechanism obtained can be shrunk further by reaction lumping, taking into account the rate-limiting steps, fast equilibrium conditions, quasi-stationary species, and parallel reactions. Another possibility for the reduction of the size of reaction mechanisms is species lumping. Recently, new methods were published for the analysis of lumping [157,158,170,174,175].

Table 1

Column numbers refer to: (1) short name of complex reaction mechanism studied; (2) number of species; (3) number of reactions; (4) references; (5) sensitivity method applied (see abbreviations); (6) aim or short description of the investigation

(1)	(2)	(3)	(4)	(5)	(6)
Pyrolysis					
High temperature propane pyrol.	14	44	[31]	BF	feature sensitivity
			[159]	BF	feature sensitivity
	11	22	[33]	AEM	test of the method
	14	66	[91]	QSA, PCA	mechanism reduction
			[120]	RA, PCA	mechan. invest. & reduct.
Low temperature propane pyrol.	38	98	[75]	GFM	mechanism investigation
			[70]	GFM	numerical test
			[122]	RA, PCA	mechanism reduction
Hexane pyrolysis	11	38	[27]	BF	numerical example
Ethane pyrolysis	7	5	[45]	AIM, (GFM, DM)	numerical test
			[22]	DM, (AIM, BF)	numerical test
			[76]	AIM	parametric scaling
			[47]	DM	numerical test
	15	25	[56]	DM	numerical example
	9	9	[101]	FAST	mechanism reduction
Decomposition of nitromethane	26	128	[88]	AIM	mechanism investigation
Decomposition of methane	17	36	[160]	BF	mechanism investigation
Pyrolysis of butylbenzene	29	60	[63]	DM	mechanism investigation
Combustion					
Oxidation of CH_4	14	12	[37]	DM	mechanism investigation
H_2–O_2 combustion	6	18	[97]	FAST	test of the method
	8	32	[30]	BF	feature sensitivity
	9	62	[44]	GFM	mechanism investigation
$H_2/O_2/N_2$ flame	8	34	[41]	DM	mechanism investigation
High temperature air reactions	5	10	[97]	FAST	test of the method
CH_4–O_2/Ar system	13	46	[106]	FAST	mechanism investigation
			[43]	GFM	numerical test
			[15]	AIM	numerical test
CS_2–O_2 explosion	10	11	[130]	BF	feature sensitivity
Methane–air flame	13	36	[161]	BF	feature sensitivity
Formaldehyde oxidation	15	25	[43]	GFM, (DM)	numerical test
			[22]	DM, (BF, AIM)	numerical test
			[51]	DM	numerical test
			[53]	DM, PCA	mech. invest. & reduct.
			[120]	RA, PCA	mech. invest. & reduct.
Oxidation of cyanogen	11	15	[28]	BF	feature sensitivity
Oxidation of methane	20	56	[105]	FAST	example of the method
Cs flare reaction	6	10	[38]	PAM, (DM)	numerical test

Table 1 (continued)

(1)	(2)	(3)	(4)	(5)	(6)
Combustion					
Wet oxidation of CO	12	52	[12]	AIM, (GFM,DM,BF)	numerical test
			[72]	AIM	feature sensitivity
			[47]	DM	numerical test
			[15]	AIM	numerical test
	8	10	[74]	AIM	derived sensitivities
	12	54	[162]		uncertainty analysis
Oxidation of N_2	5	10	[101]	FAST	mechanism reduction
Oxidation of *n*-butane			[15]	AIM	mechanism investigation
Oxidation of acetaldehyde		302	[15]	AIM	mechanism investigation
Cl_2 inhibited CO/H_2 flame	19	128	[132]	BF	feature sensitivity
Steady state CH_4/O_2 flame	25	174	[26]	BF	feature sensitivity
Premixed H_2-air flame I	8	38	[93]	NM	mech. invest. & reduct.
Premixed H_2-air flame II	8	38	[61]	DM, PCA	mech. invest. & reduct.
B/O/H/C combustion	19	118	[85]	AIM	mechanism investigation
			[86]	AIM	mechanism investigation
Thermolysis of methanol	13	16	[163]	BF	mechanism investigation
Oxidation of methane	19	61	[171]	DM	mechanism investigation
			[172]	DM	mechanism investigation
	21	69	[173]	BF	feature sensitivity
Atmospheric chemistry and photochemical smog					
Smog mechanism (Dodge et al.)	20	31	[25]	BF	uncertainty analysis
Chapman mechanism	3	4	[42]	DM, FS	numerical example
			[43]	GFM	numerical test
			[64]	SGFM/II	numerical test
			[77]	SGFM/II	mechanism reduction
			[38]	PAM, (DM)	numerical test
			[51]	DM	numerical test
Stratospheric model		55	[115]	MC	uncertainty analysis
			[116]	MC	uncertainty analysis
Smog mechanism (McRae et al.)	31	56	[107]	FAST	mech. invest., uncert. anal.
			[22]	DM, (AIM, BF)	numerical test
Photolysis of $CO-NO_x-H_2O$ mixture in air	13	10	[112]	SSA	test of the method
Smog mechanism (Stockwell and Calvert)	62	130	[68]	SOF	mechanism investigation
Sulfate production in clouds	30	34	[78]	AIM	mechanism investigation
Smog mechanism (CBM-IV)			[110]	BF, FAST	mechanism investigation
Reactions of unpolluted air	22	60	[91]	QSA, PCA	mechanism reduction
			[164]	DM, RA, PCA	mechanism reduction
Reactions in clouds	69	182	[24]	BF, DM	mech. invest. & reduct.
Sulfate production in clouds			[165]		

Table 1 (continued)

(1)	(2)	(3)	(4)	(5)	(6)
Oscillating reactions					
Brusselator	2	4	[9]	FAST	numerical example
			[82]	FS, GFM	sensitivity of limit cycles
			[143]	FS	without numerical solution
			[83]	GFM	network sensitivity analysis
			[84]	GFM	stability analysis
			[126]	F	feature sensitivity
Oregonator	3	5	[81]	GFM	feature sensitivity
			[51]	DM	numerical test
			[89]	PAM	numerical test
Lotka model	2	4	[128]	GFA	feature sensitivity
			[80]	GFM	separation of the secular term
BR reaction	12	36	[79]	GFM	feature sensitivity
	8	15	[166]	RA	mechanism reduction
BZ reaction (EFN model)	13	32	[71]	GFM	feature sensitivity
			[54]	DM, PCA	mech. invest. &reduct.
			[121]	RA, PCA	mech. invest. & reduct.
BZ reaction	11	17	[57]	DM	feature sensitivity
(both high and low sets)			[58]	DM	AI interpretation
BZ reaction	25	80	[168]	RA, PCA	mech. invest. & reduct.
Other systems					
H_2–F_2 chemical laser	15	136	[10]	FAST	mechanism investigation
Michaelis–Menten model	4	3	[104]	FAST	mechanism investigation
ASN enzyme model	8	16	[104]	FAST	mech. invest. & reduct.
Frieden enzyme model	6	12	[104]	FAST	mechanism investigation
N_2O decomposition	7	9	[66]	SGFM/II	numerical test
H_2–Br_2 reaction	5	5	[53]	DM, PCA	numerical example
CH_3/O_2 system	5	8	[73]	AIM	error analysis
$H_2CO + OH$ reaction	15	17	[87]	AIM	error analysis
lignin yellowing	58	91	[167]	BF	mech. invest. & reduct.

List of abbreviations: AEM: approximate empirical model method; AI: artificial intelligence; AIM: analytically integrated Magnus modification of the GFM; ASN: Ainslie, Shill and Neet; BF: brute force method; BR: Briggs–Rauscher; BZ: Belousov–Zhabotinsky; DM: direct method; EFN: Edelson–Field–Noyes; F: Floquet theorem; FAST: Fourier amplitude sensitivity test; FS: functional sensitivity investigation (including sensitivity density); GFA: global feature sensitivity analysis; GFM: Green function method; MC: Monte Carlo method; NM: Newton method for the solution of sensitivity equations for a two-point boundary value problem; PCA: principal component analysis; QSA: quasi-stationary sensitivity analysis; RA: rate analysis (analysis of matrix $\tilde{\mathbf{F}}$); SGFM: scaled Green function method; SOF: direct calculation of the sensitivity of objective functions; SS: stationary sensitivities; SSA: stochastic sensitivity analysis.

7. Concluding remarks

At present the theory of sensitivity analysis has achieved an advanced level, and efficient numerical realizations are also available. However, sensitivity analysis has not been applied as extensively as would be desirable and possible. Although in the last few years several papers were published in which sensitivity methods were applied, in most of the papers that have so far appeared in this field, the sensitivity methods and not the reaction systems were the subjects of investigation. In this review, not only are the theoretical and numerical tools of sensitivity analysis enumerated, but also their practical applications are dealt with in detail. Hence, it is hoped that this paper may help to bridge the gap between theory and application of sensitivity analysis in chemical kinetics.

Acknowledgements

The author is indebted to Professor T. Bérces and to Drs. J. Tóth and P. Valkó for their careful reading of the manuscript and for many helpful suggestions. It is also gratefully acknowledged that Professor H. Rabitz called the author's attention to several recently submitted papers.

References

[1] J.-T. Hwang, in: *Chemical Kinetics of Small Organic Radicals*, Vol. 2, ed. Z.B. Alfassi (CRC Press, Boca Raton, 1988), p. 149.
[2] M. Frenklach, in: *Combustion Chemistry*, ed. W.C. Gardiner, Jr. (Springer, New York, 1984).
[3] D. Edelson, Science 214(1981)981.
[4] C.K. Westbrook and F.L. Dryer, Prog. Energy Combust. Sci. 10(1984)1.
[5] M.J. Pilling, in: *Modern Gas Kinetics*, ed. M.J. Pilling and I.W.M. Smith (Blackwell, Oxford, 1987), p. 303.
[6] P. Érdi and J. Tóth, *Mathematical Models of Chemical Reactions: Theory and Applications of Deterministic and Stochastic Models* (Manchester University Press, Manchester, 1989).
[7] J.I. Steinfeld, J.S. Francisco and W.L. Hase, *Chemical Kinetics and Dynamics* (Prentice–Hall, Englewood Cliffs, NJ, 1989).
[8] H. Rabitz, M. Kramer and D. Dacol, Ann. Rev. Phys. Chem. 34(1983)419.
[9] J.W. Tilden, V. Costanza, G.J. McRae and J.H. Seinfeld, in: *Modelling of Chemical Reaction Systems*, ed. K.H. Ebert, P. Deuflhard and W. Jäger (Springer, Berlin, 1981), p. 69.
[10] R.I. Cukier, H.B. Levine and K.E. Shuler, J. Comp. Phys. 26(1978)1.
[11] H. Rabitz, Comp. Chem. 5(1981)167.
[12] M.A. Kramer, H. Rabitz, J.M. Calo and R.J. Kee, Int. J. Chem. Kinet. 16(1984)559.
[13] D. Edelson and H. Rabitz, in: *Oscillations and Traveling Waves in Chemical Systems*, ed. R.J. Field and M. Burger (Wiley, New York, 1987), p. 193.
[14] H. Rabitz, Chem. Rev. 87(1987)101.
[15] A.K. Hayashi and T. Fujiwara, Mem. Faculty of Eng., Nagoya University 38(1986)86.
[16] H. Rabitz, Science 246(1989)221.
[17] H. Rabitz, Physica 20D(1986)67.
[18] R. Tomović and M. Vukobratović, *General Sensitivity Theory* (Elsevier, New York, 1972).
[19] P.M. Frank, *Introduction to System Sensitivity Theory* (Academic Press, New York, 1978).

[20] L. Eno and H. Rabitz, Adv. Chem. Phys. 51(1982)177.
[21] S.H. Shi and H. Rabitz, Comp. Phys. Rep. 10(1989)3.
[22] A.M. Dunker, J. Chem. Phys. 81(1984)2385.
[23] A.M. Dunker, Atm. Environ. 15(1981)1155.
[24] S.N. Pandis and J.H. Seinfeld, J. Geophys. Res. 94(1989)1105.
[25] M.C. Dodge and T.A. Hecht, Int. J. Chem. Kinet. S1(1975)155.
[26] J.O. Olsson and L.L. Andersson, Combust. Flame 67(1987)99.
[27] K.H. Ebert, H.J. Ederer and G. Isbarn, Angew. Chem. Int. Ed. Engl. 19(1980)333.
[28] A. Lifshitz and M. Frenklach, Int. J. Chem. Kinet. 12(1980)159.
[29] R.J. Gelinas and P.D. Skewes-Cox, J. Phys. Chem. 81(1977)2468.
[30] M.W. Slack, Combust. Flame 28(1977)241.
[31] T. Koike and W.C. Gardiner, Jr., J. Phys. Chem. 84(1980)2005.
[32] J. Warnatz, *18th Symp (Int.) on Combustion* (1981), p. 369.
[33] D. Miller and M. Frenklach, Int. J. Chem. Kinet. 15(1983)677.
[34] M. Frenklach and D.L. Miller, AIChE J. 31(1985)498.
[35] M. Frenklach, Combust. Flame 58(1984)69.
[36] R. Derwent and Ø. Hov, J. Geophys. Res. (Atm.) 93(1988)5185.
[37] F.A. Buhman, V.G. Melamed, L.S. Polak, Yu.L. Haut and E.N. Chervochkin, in: *Primenenie Vychislitel'noi Matematiki v Himicheskoi i Fizicheskoi Kinetike*, ed. L.S. Polak (Nauka, Moscow, 1969), p. 12.
[38] J.-T. Hwang, Int. J. Chem. Kinet. 15(1983)959.
[39] J.-T. Hwang, E.P. Dougherty, S. Rabitz and H. Rabitz, J. Chem. Phys. 69(1978)5180.
[40] J.-T. Hwang, Proc. Natl. Sci. Council B. ROC 6(1982)20.
[41] T.P. Coffee and J.M. Heimerl, Combust. Flame 50(1983)323.
[42] R.P. Dickinson and R.J. Gelinas, J. Comp. Phys. 21(1976)123.
[43] E.P. Dougherty, J.-T. Hwang and H. Rabitz, J. Chem. Phys. 71(1979)1794.
[44] E.P. Dougherty and H. Rabitz, J. Chem. Phys. 72(1980)6571.
[45] M.A. Kramer, J.M. Calo and H. Rabitz, Appl. Math. Modelling 5(1981)432.
[46] R.W. Atherton, R.B. Schainker and E.R. Ducot, AIChE J. 21(1975)441.
[47] J.R. Leis and M.A. Kramer, ACM Trans. Math. Softw. 14(1988)45.
[48] J.R. Leis and M.A. Kramer, ACM Trans. Math. Softw. 14(1988)61.
[49] J.R. Leis and M.A. Kramer, Comput. Chem. Eng. 9(1985)93.
[50] M. Caracotsios and W.E. Stewart, Comput. Chem. Eng. 9(1985)359.
[51] P. Valkó and S. Vajda, Comp. Chem. 8(1984)255.
[52] M. Koda, A.H. Dogru and J.H. Seinfeld, J. Comp. Phys. 30(1979)259.
[53] S. Vajda, P. Valkó and T. Turányi, Int. J. Chem. Kinet. 17(1985)55.
[54] S. Vajda and T. Turányi, J. Phys. Chem. 90(1986)1664.
[55] Y. Reuven, M.D. Smooke and H. Rabitz, J. Comp. Phys. 64(1986)27.
[56] O.A. Asbjornsen, in: *Proc. Conf. CHEMPLANT'80*, Hévíz, Hungary (Budapest, 1980) Vol. 2, p. 723.
[57] L. Györgyi, T. Deutsch and E. Körös, Int. J. Chem. Kinet. 19(1987)35.
[58] L. Györgyi, T. Deutsch and E. Körös, Int. J. Chem. Kinet. 19(1987)435.
[59] I.M. Thomas and C. Kiparissides, J. Appl. Pol. Sci. 29(1984)2195.
[60] A.M. Dunker, Atm. Environ. 20(1986)479.
[61] S. Vajda, H. Rabitz and R.A. Yetter, Combust. Flame, in press.
[62] T.M. Zamis, L.J. Parkhurst and G.A. Gallup, Comput. Chem. 13(1989)165.
[63] H. Freund and W.N. Olmstead, Int. J. Chem. Kinet. 21(1989)561.
[64] J.-T. Hwang, Proc. Natl. Sci. Council B. ROC 6(1982)37.
[65] J.-T. Hwang, Proc. Natl. Sci. Council B. ROC 6(1982)166.
[66] J.-T. Hwang and Y.-S. Chang, Proc. Natl. Sci. Council B. ROC 6(1982)308.
[67] C. Seigneur, G. Stephanopoulos and R.W. Carr, Jr., Chem. Eng. Sci. 37(1982)845.

[68] O. Gautier, R.W. Carr, Jr. and C. Seigneur, Int. J. Chem. Kinet. 17(1985)1347.
[69] E.P. Dougherty and H. Rabitz, Int. J. Chem. Kinet. 11(1979)1237.
[70] D. Edelson, L.C. Kaufman and D.D. Warner, in: *ACS Symp. Ser. No. 173: Supercomputers in Chemistry*, ed. P. Lykos and I. Shavitt (1981).
[71] D. Edelson, Int. J. Chem. Kinet. 13(1981)1175.
[72] R.A. Yetter, F.L. Dryer and H. Rabitz, Combust. Flame 59(1985)107.
[73] M.J. Pilling and M.J.C. Smith, J. Phys. Chem. 89(1985)4713.
[74] R.A. Yetter, L.A. Eslava, F.L. Dryer and H. Rabitz, J. Phys. Chem. 88(1984)1497.
[75] D. Edelson and D.L. Allara, Int. J. Chem. Kinet. 12(1980)605.
[76] M.A. Kramer, H. Rabitz and J.M. Calo, Appl. Math. Modelling 8(1984)341.
[77] J.-T. Hwang, Proc. Natl. Sci. Council B. ROC 6(1982)270.
[78] S.-Y. Cho and G.R. Carmichael, Atm. Environ. 20(1986)1959.
[79] D. Edelson, J. Phys. Chem. 87(1983)1204.
[80] R. Larter, J. Phys. Chem. 87(1983)3114.
[81] D. Edelson and V.M. Thomas, J. Phys. Chem. 85(1981)1555.
[82] R. Larter, H. Rabitz and M. Kramer, J. Chem. Phys. 80(1984)4120.
[83] R. Larter and B.L. Clarke, J. Chem. Phys. 83(1985)108.
[84] R.M. Hedges, Jr. and H. Rabitz, J. Chem. Phys. 82(1985)3674.
[85] R.A. Yetter, H. Rabitz, F.L. Dryer, R.C. Brown and C.E. Kolb, Combust. Flame, submitted.
[86] R.A. Yetter, S.Y. Cho, H. Rabitz, F.L. Dryer, R.C. Brown and C.E. Kolb, *22nd Symp. (Int.) on Combustion* (1988), p. 919.
[87] R.A. Yetter, H. Rabitz, F.L. Dryer, R.G. Maki and R.B. Klemm, J. Chem. Phys. 91(1989)4088.
[88] R.A. Yetter and H. Rabitz, Modeling and sensitivity analysis of homogeneous, gas-phase, nitromethane decomposition, to be published.
[89] J.-T. Hwang, J. Chin. Chem. Soc. 32(1985)253.
[90] W. Schellong and C. Schuhler, Z. phys. Chemie (Leipzig) 267(1986)15.
[91] T. Turányi, T. Bérces and J. Tóth, J. Math. Chem. 2(1988)401.
[92] H. Rabitz and M.D. Smooke, J. Phys. Chem. 92(1988)1110.
[93] M.D. Smooke, H. Rabitz, Y. Reuven and F.L. Dryer, Combust. Sci. Tech. 59(1988)295.
[94] C. Wulfman and H, Rabitz, J. Phys. Chem. 90(1986)2264.
[95] L.M. Hubbard, C. Wulfman and H. Rabitz, J. Phys. Chem. 90(1986)2273.
[96] R.I. Cukier, C.M. Fortuin, K.E. Shuler, A.G. Petschek and J.H. Schaibly, J. Chem. Phys. 59(1973)3873.
[97] J.H. Schaibly and K.E. Shuler, J. Chem. Phys. 59(1973)3879.
[98] R.I. Cukier, J.H. Schaibly and K.E. Shuler, J. Chem. Phys. 63(1975)1140.
[99] R.I. Cukier, H.B. Levine and K.E. Shuler, J. Phys. Chem. 81(1977)2365.
[100] K. Kanatani, Inform. Control 47(1980)37.
[101] T.M. Grigoryeva, Yu.A. Kolbanovskii, A.A. Levickii, L.S. Polak and R.L. Tatuzov, Kinet. Katal. 26(1985)1307.
[102] M. Koda, G.J. McRae and J.H. Seinfeld, Int. J. Chem. Kinet. 11(1979)427.
[103] G.J. McRae, J.W. Tilden and J.H. Seinfeld, Comput. Chem. Eng. 6(1982)15.
[104] T.H. Pierce, R.I. Cukier and J.L. Dye, Math. Biosci. 56(1981)175.
[105] V.G. Gorskii, V.I. Dimitrov and V.I. Golovichev, Him. Fiz. (1983)1046.
[106] A.A. Boni and R.C. Penner, Combust. Sci. Tech. 15(1977)99.
[107] A.H. Falls, G.J. McRae and J.H. Seinfeld, Int. J. Chem. Kinet. 11(1979)1137.
[108] J.W. Tilden and J.H. Seinfeld, Atm. Environ. 16(1982)1357.
[109] T. O'Brien and T.H. Pierce, Chem. Phys. Processes Combust. (1981)77.
[110] E. Joos, A. Mendonça and C. Seigneur, Atm. Environ. 21(1987)1331.
[111] T.H. Pierce and R.I. Cukier, J. Comp. Phys. 41(1981)427.
[112] V. Costanza and J.H. Seinfeld, J. Chem. Phys. 74(1981)3852.
[113] R.R. Lucchese, J. Chem. Phys. 83(1985)3118.

[114] C.B. Smith and R.R. Lucchese, J. Chem. Phys. 87(1987)4170.
[115] R.S. Stolarski, D.M. Butler and R.D. Rundel, J. Geophys. Res. 83(1978)3074.
[116] R.S. Stolarski and A.R. Douglass, J. Geophys. Res. 91(1986)7853.
[117] D.H. Ehhalt, J.S. Chang and D.M. Butler, J. Geophys. Res. 84(1979)7889.
[118] R.G. Derwent, Atm. Environ. 21(1987)1445.
[119] W.J. Ray, Jr., Biochem. 22(1983)4625.
[120] T. Turányi, T. Bérces and S. Vajda, Int. J. Chem. Kinet. 21(1989)83.
[121] T. Turányi, Acta Chim. Hung., to be published.
[122] T. Turányi, New J. Chem., in press.
[123] P.C. Fife, J. Phys. Chem. 85(1981)2861.
[124] D. Edelson, J. Phys. Chem. 85(1981)2861.
[125] M.A. Kramer, H. Rabitz and J.M. Calo, Appl. Math. Modelling 8(1984)328.
[126] R. Larter, J. Chem. Phys. 85(1986)7127.
[127] J.G.B. Beumeé, L. Eno and H. Rabitz, J. Comp. Phys. 57(1985)318.
[128] M. Skumanich and H. Rabitz, Commun. in J. Mol. Sci. 2(1982)79.
[129] R.A. Yetter, F.L. Dryer and H. Rabitz, Chem. Phys. Proc. Combust., Paper 35 (1985).
[130] W.C. Gardiner, Jr., J. Phys. Chem. 81(1977)2367.
[131] W.C. Gardiner, Jr., J. Phys. Chem. 83(1979)37.
[132] W.D. Chang, S.B. Karra and S.M. Senkan, Combust. Flame 69(1987)113.
[133] D.G. Cacuci, J. Math. Phys. 22(1981)2794.
[134] D.G. Cacuci, J. Math. Phys. 22(1981)2803.
[135] A.M. Dunker, Atm. Environ. 14(1980)671.
[136] M. Demiralp and H. Rabitz, J. Chem. Phys. 74(1981)3362.
[137] D.K. Dacol and H. Rabitz, J. Chem. Phys. 78(1983)4905.
[138] M. Demiralp and H. Rabitz, J. Chem. Phys. 75(1981)1810.
[139] R. Larter, H. Rabitz and M. Kobayashi, J. Chem. Phys. 79(1983)692.
[140] M. Koda, Atm. Environ. 16(1982)2595.
[141] H. Rabitz, in: *Lecture Notes in Mathematics 1086: Sensitivity of functionals with applications to engineering sciences*, ed. V. Komkov (Springer, 1984), p. 77.
[142] S.-Y. Cho, G.R. Carmichael and H. Rabitz, Atm. Environ. 21(1987)2589.
[143] C.L. Irwin and V. Komkov, J. Opt. Theor. Appl. 44(1984)569.
[144] D.K. Dacol and H. Rabitz, J. Math. Phys. 25(1984)2716.
[145] L. Eno, J.G.B. Beumeé and H. Rabitz, Appl. Math. Comp. 16(1985)153.
[146] R. Larter, Stud. Phys. Theor. Chem. 28(1984)371.
[147] R. Larter, in: *Chemical Instabilities*, ed. G. Nicolis and F. Baras (Reidel, Dordrecht, 1984), p. 59.
[148] M.A. Kramer, J.M. Calo, H. Rabitz and R.J. Kee, Report SAND82-8231, Sandia National Laboratories (1982).
[149] R.J. Kee, J.A. Miller and T.H. Jefferson, Report SAND80-8003, Sandia National Laboratories (1980).
[150] M.A. Kramer, R.J. Kee and H. Rabitz, Report SAND82-8230, Sandia National Laboratories (1982).
[151] A.E. Lutz, R.J. Kee and J.A. Miller, Report SAND87-8248, Sandia National Laboratories (1988).
[152] T. Turányi, Comput. Chem., in press.
[153] D.M. Butler, Geophys. Res. Lett. 5(1978)769.
[154] P. Valkó and S. Vajda, *Advanced Scientific Computing in BASIC* (Elsevier, Amsterdam, 1989).
[155] A.R. Marsden, Jr., M. Frenklach and D.D. Reible, JAPCA 37(1987)370.
[156] J.A. Miller, M.C. Branch, W.J. McLean, D.W. Chandler, M.D. Smooke and R.J. Kee, *20th Symp. (Int.) on Combustion* (1984), p. 673.
[157] G. Li and H. Rabitz, Chem. Eng. Sci. 44(1989)1413.
[158] G. Li and H. Rabitz, Chem. Eng. Sci. 45(1990)977.
[159] J.M. Simmle, W.C. Gardiner, Jr. and C.S. Eubank, J. Phys. Chem. 86(1982)799.

[160] J.M. Roscoe and M.J. Thompson, Int. J. Chem. Kinet. 17(1985)967.
[161] N. Peters and W. Hocks, in: *Gasdynamic and Chemical Lasers*, ed. M. Fiebig and H. Hügel (DFVLR-Press, Köln-Porz, 1977).
[162] R.A. Yetter, F.L. Dryer and H. Rabitz, Combust. Sci. Tech., submitted.
[163] I. Börger, J. Lachmann, H.-J. Spangenberg and W. Fiebig, Z. phys. Chem. (Leipzig) 270(1989)458.
[164] T. Turányi and T. Bérces, React. Kinet. Catal. Lett. 41(1990)103.
[165] G.R. Taylor, J. Atm. Sci. 46(1989)1991.
[166] T. Turányi, React. Kinet. Catal. Lett., in press.
[167] H. Tylli, C. Olkkonen and I. Forsskåhl, J. Photochem. Photobiol. A: Chem. 49(1989)397.
[168] T. Turányi, L. Györgyi and R.J. Field, J. Phys. Chem., to be published.
[169] C.E. Wulfman and H. Rabitz, J. Math. Chem. 3(1989)243.
[170] C.E. Wulfman and H. Rabitz, J. Math. Chem. 3(1989)261.
[171] V.I. Vedeneev, M.Ya. Goldenberg, N.I. Gorban and M.A. Teytalboym, Kinet. Katal. 29(1988)14.
[172] V.I. Vedeneev, M.Ya. Goldenberg, N.I. Gorban and M.A. Teytelboym, Kinet. Katal. 29(1988)1291.
[173] V.I. Vedeneev, M.Ya. Goldenberg, N.I. Gorban, A.A. Karnauk and M.A. Teytelboym, Kinet. Katal. 29(1988)1297.
[174] G. Li and H. Rabitz, Chem. Eng. Sci., in press.
[175] G. Li and H. Rabitz, Chem. Eng. Sci., submitted.