Systems Analysis at the Molecular Scale

HERSCHEL RABITZ

Problems involving physiochemical phenomena on both the microscopic and macroscopic scales often raise similar sets of generic issues and questions. The complexity of these problems is beginning to make inoperative the traditional intuition-based approaches to their analysis and solution. The common characteristics of large, multi-variable, complex molecular systems call for a new, more systematic approach to guide theoretical and experimental efforts. With mathematical modeling becoming an essential ingredient in the studies, it is argued that molecular systems analysis and especially the systematic tools of sensitivity analyis can play an increasingly important role in understanding and finding solutions to complex, chemically based problems.

P HENOMENA HAVING A CHEMICAL ORIGIN ARE UBIQUI-
tious, and in recent years problems of ever larger complexity
have been receiving careful attention by the chemical commu-
nity. In the past it was thought possible to isolate small pieces of
large-scale problems for analysis with the hope that the results could
be reassembled into an overall framework. Unfortunately, the
phenomena of interest often involve strongly coupled components
including nonlinear interactions, which require that the system
ultimately be studied as a whole. Furthermore, macroscopic observ-
able behavior can be directly dictated by events happening on
ultrafast time scales on atomic dimensions. Even when these prob-
lems can be broken down into multicomponents, each one may be a
microcosm of high complexity. For example, molecular dynamics as
a subcomponent of some macroscopic process such as atmospheric
dynamics is itself a highly coupled, multivariable system.

Problems that fall into the category described above include drug
and catalyst design, the determination of biomolecular structure,
reactive flow (as in the atmosphere, combustion, industrial process-
es), and control of molecular motion. The phenomena of interest
and the goals in such studies span a variety of seemingly unrelated
issues. However, a number of common questions always seem to
arise, suggesting that a family of generic tools might be transferable
from one area to another. It is becoming increasingly more impor-
tant to direct theoretical and experimental efforts to ultimately yield
a computationally practical, mathematical model of the phenomena
of interest. Such models are to be used not merely for correlation
purposes but rather as a testing ground for new ideas and generally
as a means to guide further research, development, and applications.

Certainly the recent flurry of activity in biomolecular design

The author is at the Department of Chemistry, Princeton University, Princeton, NJ 08544.

stands out as a notable example. Problems of this type have often
been approached in the laboratory by what might best be called "mix
and try" solutions. Unfortunately, with the large number of varia-
bles and unknowns involved, this intuitively based approach is
prohibitively expensive and time-consuming. Theory and modeling
clearly play a central role in guiding such complex efforts. However,
it is the thesis of this article that these tools alone will themselves
become mired in a tangle of multitudinous parameters and variables
without the establishment of a systems-based approach. The efficacy
of this comment for physiochemical problems seems to have been
first appreciated by the chemical kinetics and combustion communi-
ties (1). The same tools have just as significant, if not more,
applications at the most fundamental levels of chemical-physical
phenomena.

Systems techniques have a long history, primarily in the engineer-
ing disciplines (2). Although some of the physiochemical areas of
study mentioned above ultimately border on engineering applica-
tions, the same perspective has equal significance at all levels,
including that of quantum mechanics. The application of raw
computing power alone to any of these problems does not in itself
lead to understanding, nor does it probably lead even to a practical
means for achieving some goal such as molecular design. Rather, the
modeling efforts must in turn be guided by sophisticated sensitivity
analysis techniques (1, 3) if they are to be truly useful. The judicious
application of sensitivity analysis techniques appears to be the key
ingredient needed to draw out the maximum capabilities of mathe-
matical modeling with parallel experimental efforts for solving
complex physiochemical problems. The main body of this article is
concerned with providing a status report and drawing attention to
the availability of these techniques, how they may be applied, and
where it is possible to develop further analysis techniques. Sensitiv-
ity analysis is not limited to treating problems where model
uncertainty is prevalent; rather, full knowledge of the components
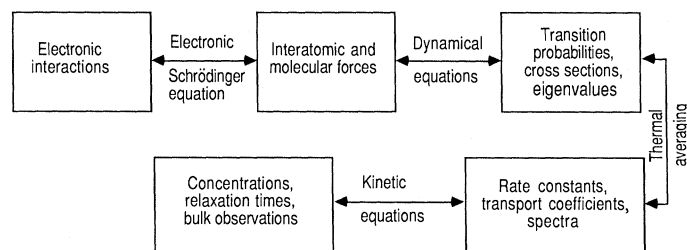that enter a physical model does not imply understanding of their

Fig. 1. Flow chart illustrating the hierarchical connection between micro-
scopic and macroscopic variables in chemical dynamics and kinetics. Sensitiv-
ity analysis techniques may be developed to specifically probe the parametric
and functional interconnections between the levels of the flow chart. The
double-headed arrows connecting elements in the flow chart imply that both
forward and inverse questions may be explored.

roles, which are most often obscured by the strong coupling that strongly influences the actual system observables.

This article is not intended to be an encompassing review of systems or of sensitivity analysis techniques in the chemical-physical domain, but I hope that it will provide sufficient detail to draw attention to their potential significance, especially in areas where they have not been seriously applied. The first section deals with sensitivity analysis tools as primarily involved with building up a physiochemical model, analyzing its content, and interfacing with laboratory observations. The second section deals with the antithetical process of reducing full detailed models to their essential or lumped structure for more ready application.

Tools of Sensitivity Analysis

Virtually all of the phenomena discussed above may be described in terms of mathematical models typically with many dependent variables $O_1(\mathbf{r},t)$, $O_2(\mathbf{r},t)$, ... and parameters $\alpha_1(\mathbf{r},t)$, $\alpha_2(\mathbf{r},t)$, ..., where $\mathbf{r}$ denotes an appropriate set of independent coordinates and t is time. The output variables $O_i(\mathbf{r},t)$ may be directly amenable to obervation in the laboratory or simply intermediate quantities such as quantum-mechanical wave functions. The parameters $\alpha_j(\mathbf{r},t)$ may be distributed in space or time, or both, and may correspond, for example, to the presence of potentials or external fields. In other cases, the parameters may be constants such as diffusion coefficients or rate constants in chemical kinetics. All of these various dependent variables and parameters may be identified as arising in a hierarchical chain depicted in Fig. 1 ranging from phenomena at the electronic structure level up to observable properties of bulk media. A basic understanding of observable phenomena in bulk media requires an understanding of the underlying processes in the other boxes ultimately ranging down to the electronic level. This point is especially important if theory and modeling are to be successfully used to guide the design of new materials (4). A significant goal is to identify which dependent variables $O_i(\mathbf{r},t)$ or parameters $\alpha_j(\mathbf{r},t)$ are critically important, how they are interrelated, and especially how such quantities at different levels in Fig. 1 influence behavior at another level. The influence of these quantities at different levels is clearly evident when one is proceeding from the micro scale to the macro scale (that is, from the left in Fig. 1), but it is also relevant in the opposite direction because most practical observations are performed at a "higher" level (that is, to the right in Fig. 1) whereas the desired information content is ultimately at a "lower" level. For example, spectroscopy and molecular beam scattering experiments are often performed for the purpose of their inversion to an intermolecular potential function.

In some cases, the parameter space may be divided into regions corresponding to bifurcated behavior of the system-dependent variables. At this point I assume that the system of interest is not of this type or at least that a subregion is being treated and that one is concerned with its accordingly local behavior. This assumption is necessary because most sensitivity analysis studies are based on gradient techniques that require the existence of derivatives of the dependent variables with respect to the system parameters. It is assumed further that a physical model (at least an initial one) has been established, its translation into a mathematical framework (typically differential equations) achieved, and its solution obtained by an appropriate algorithm. Sensitivity analysis then comes into play when one is attempting to unravel the ensuing complex relation between the input parameters and the output observables.

Various approaches to the latter problem might be taken, including the traditional avenue of rerunning a statistical ensemble of models with varied parameters (5) or perhaps other guided schemes

of parameter space variations (6). Clearly an enormous amount of information can be generated in this fashion, and it is desirable to have convenient and mathematically well-defined measures of the system sensitivity. Gradient-based techniques, in which the sensitivity coefficients (sometimes called densities) are defined as $\delta O_i(\mathbf{r},t)/\delta\alpha_j(\mathbf{r}',t')$, have proved most convenient in this regard (1, 3, 7). The quantities may be interpreted as the response of the ith observable at point $\mathbf{r}$ and time t with respect to a disturbance of the jth parameter at point $\mathbf{r}'$ and time t'. This interpretation is evident from the first-order response $\delta O_i(\mathbf{r},t)$ to a set of explicit variations $\delta\alpha_j(\mathbf{r}',t')$ given by

$$\delta O_i(\mathbf{r},t) = \sum_j \int \frac{\delta O_i(\mathbf{r},t)}{\delta\alpha_j(\mathbf{r}',t')} \, \delta\alpha_j(\mathbf{r}',t') \, d\mathbf{r}' \, dt' \tag{1}$$

Generally the emphasis in sensitivity analysis is not on the explicit introduction of any particular variations $\delta\alpha_j(\mathbf{r}',t')$ and performance of the integral in Eq. 1 but rather on the computation and examination of the sensitivity coefficients $\delta O_i(\mathbf{r},t)/\delta\alpha_j(\mathbf{r}',t')$, as they are independent of any special variations in the parameters. These coefficients provide a detailed map connecting regions of the input parameter space to that of the output observable space. Cases may arise where $\mathbf{r}$ and $\mathbf{r}'$ are in reference to different spaces (for example, with $\mathbf{r}'$ being the n-dimensional coordinates of an intermolecular potential $V(\mathbf{r}')$ and $\mathbf{r}$ being the ordinary three-dimensional coordinates of a chemical concentration $C(\mathbf{r})$. Similarly, t and t' may be in reference to different time scales arising, for example, on macro and micro levels. Thus the sensitivity coefficients can reveal the physical-chemical connections possibly occurring on vastly different length and time scales in Fig. 1.

Although Eq. 1 indicates that this is a linear variational analysis, it is performed on the nominal full solution to the physical problem. This point is significant even in the simplest case of a physical problem described by linear equations (such as Schrödinger's equation), where the output is still a highly complex nonlinear functional of the input parameters or potential. The functional dependence arises as a result of a mapping of the entire input function onto each point of the output. For problems where the parameters are constants (that is, independent of $\mathbf{r}'$ and t') the functional response embodied in Eq. 1 reduces to ordinary multivariable calculus

$$dO_i(\mathbf{r},t) = \sum_j \frac{\partial O_i(\mathbf{r},t)}{\partial\alpha_j} \, d\alpha_j \tag{2}$$

where the parametric sensitivity coefficients are now $\partial O_i(\mathbf{r},t)/\partial\alpha_j$ and have an analogous meaning to those above. The sign and the magnitude of the sensitivity coefficients or densities as functions of position or time or both represent their information content. For example, if the output observable is a rate constant k and the input is a potential surface $V(\mathbf{r})$ among the reacting particles, then $\delta k/\delta V(\mathbf{r})$ is a function of the same coordinates $\mathbf{r}$ as the potential. Thus, a contour plot of $\delta k/\delta V(\mathbf{r})$ superimposed on $V(\mathbf{r})$ would indicate the regions of significance in the potential for the particular rate constant. The sensitivity coefficients provide additional information that is not directly available from solving the model equations alone. Although each physiochemical problem has its own characteristics and resultant mathematical model, the equations that determine the sensitivity coefficients have a common structure. In general, chemical-physical phenomena may be modeled by equations that have the following symbolic form

$$L_n(\alpha,O) = 0 \tag{3}$$

where L_n, $n = 1, 2, \ldots$, might correspond to the nth member of a set of nonlinear differential equations determining the vector of output $O(\mathbf{r},t)$. Associated initial or boundary conditions or both would be needed to uniquely specify the model equations. The

sensitivity equations are obtained by taking the first variation of Eq. 3, and, for the case of the parametric sensitivity coefficients entering into Eq. 2, the result is

$$\sum_i \left(\frac{\partial L_n}{\partial O_i} \right) \frac{\partial O_i}{\partial \alpha_j} + \frac{\partial L_n}{\partial \alpha_j} = 0 \qquad (4)$$

A similar equation may be found for the functional sensitivity coefficients in Eq. 1.

The first task in executing a sensitivity analysis is to compute the sensitivity coefficients for a given problem. Codes for solving Eq. 4 have been written for various applications in reactive flows (8), classical (9) and quantum molecular dynamics (10), spectroscopy (11), and equilibrium molecular structure (12). The detailed algorithms are not described here, although the efficiency of such coding depends on how the original physical problem is set up and solved. Given the desire to obtain the valuable sensitivity information, it is important to keep in mind the method of setting up and solving the problem when one is approaching a new class of problems for computational coding. As an example, if the solution process for Eq. 3 directly involves the computation of the system Jacobian matrix $\partial L_n/\partial O_i$, then there is an immediate computational savings in solving Eq. 4, as it also requires the Jacobian input.

Sensitivity coefficients have been computed for a number of physical problems involving chemical phenomena, ranging from issues at the electronic structure level through collision dynamics up to macroscopic kinetics. Indeed, a critical question concerns how interactions or parameters at the most fundamental electronic or intermolecular level as well as intramolecular force field levels ultimately manifest themselves in the properties of bulk media. We are only at the beginnings of such an understanding now, but it is anticipated that at least in some prototypical problems this full mapping through sensitivity analysis will be carried out in the near future. In going from the left to the right in Fig. 1, a series of sequential problems are solved, which allow the output sensitivity at one stage to be used as the input sensitivity at the next stage. This process produces a chain rule extension of the relation in Eq. 1 connecting the hierarchical flow. For example, consider the case where the observable of interest is a relaxation time τ in a bulk gaseous medium characterized by a fixed temperature T. The medium consists of molecules interacting through an intermolecular potential $V(\mathbf{r})$. A physically interesting question concerns the relation between τ and $V(\mathbf{r})$ giving rise to the relaxation process. Therefore, we have

$$\frac{\delta \tau}{\delta V(\mathbf{r})} = \sum_{ij} \int \left[\frac{\partial \tau}{\partial k_{ij}(T)} \right] \left[\frac{\delta k_{ij}(T)}{\delta \sigma_{ij}(E)} \right] \left[\frac{\delta \sigma_{ij}(E)}{\delta V(\mathbf{r})} \right] dE \qquad (5)$$

where $k_{ij}(T)$ is the macroscopic rate constant connecting the ith and jth quantum levels of the system, and $\sigma_{ij}(E)$ is the corresponding collision cross section at energy E. Equation 5 may be further simplified in that
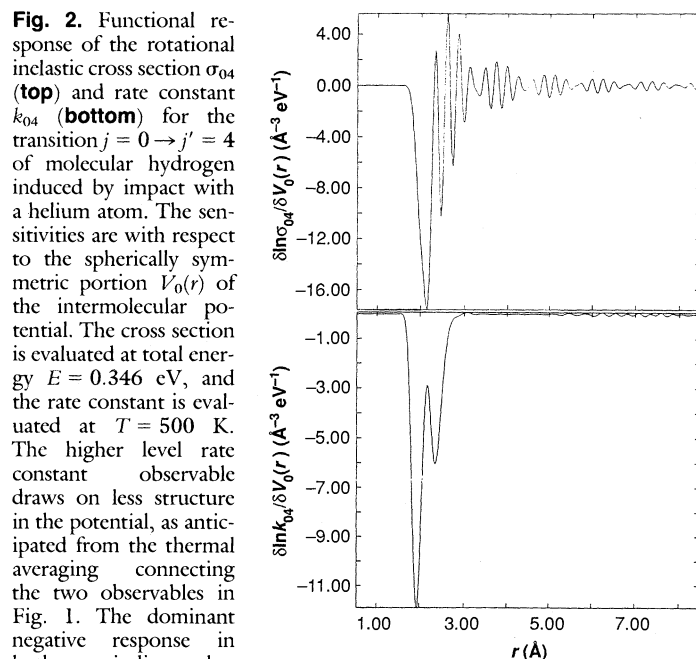
$$\delta k_{ij}(T)/\delta \sigma_{ij}(E) = \sqrt{E} \, P(E,T)$$

where $P(E,T)$ is a Boltzmann velocity distribution function for the medium. The two remaining sensitivities, $\partial \tau/\partial k_{ij}(T)$ and $\delta \sigma_{ij}(E)/\delta V(\mathbf{r})$, may be separately computed by solving Eqs. 3 and 4, respectively, for the relaxation process and collision dynamics.

This hierarchical chain relation ultimately allows for relating electronic structure to macroscopic properties. For example, it should be feasible to quantitatively assess how electronic orbitals "steer" reactants to their final product. A simple glimpse at what may arise is shown in Fig. 2 for the rotational inelastic collision of helium and hydrogen (13). Here, the two levels of observables involve collision cross sections and rate constants, with the latter quantities being a thermal average of the cross sections. In both
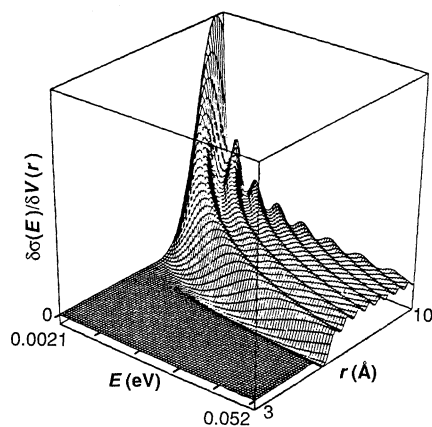
cases, the desire is to understand the role of structure in the potential surface. The natural expectation is to see less structure in the sensitivity for higher level observables with respect to the input potential than for lower level observables. Although this response is confirmed in this case, an important question concerns whether this expectation may break down in other situations. A reasonable conjecture is that this might be the case for observables that arise from quantum phase-interference phenomena. Even for systems that produce a gradual loss of information in going from one level to another in Fig. 1, the sensitivities provide a quantitative measure of this flow. A simple glance at the structure in Fig. 2 shows that the detailed relation defies intuition. Although in many cases a qualitative understanding of the overall sign or even magnitude of the sensitivities can be argued, invariably even the simplest problems have proved to contain interesting and unusual puzzles. For example, in Fig. 3 the sensitivity of the total integrated elastic cross section with respect to a purely repulsive model potential between two interacting atoms is shown (14). The surprise in Fig. 3 is the negative sensitivity region, which implies that making the potential more repulsive in some instances may make the cross section smaller. This is akin to stating, contrary to the common wisdom, that as the barn door becomes bigger, it becomes harder to hit.

In addition to its application in quantum and classical molecular dynamics, chemical system sensitivity analysis has been carried out in various problems involving reactive flows where the input is at the level of parameters in a continuum model of kinetics and transport (7, 8). An example taken from a hydrogen-oxygen one-dimensional premixed laminar flame is shown in Fig. 4 (15). In this system, the kinetics are highly exothermic and additional feedback or coupling exists as a result of the presence of mass and thermal diffusion. Naturally, the model or physical mechanism in any reactive flow is set up such that each of the kinetic or transport parameters is at least thought to be independent. Similarly, the chemical species are certainly chosen for their completeness as distinct physical variables, barring conservation-of-mass constraints.

Fig. 2. Functional response of the rotational inelastic cross section σ_{04} (**top**) and rate constant k_{04} (**bottom**) for the transition $j = 0 \rightarrow j' = 4$ of molecular hydrogen induced by impact with a helium atom. The sensitivities are with respect to the spherically symmetric portion $V_0(r)$ of the intermolecular potential. The cross section is evaluated at total energy $E = 0.346$ eV, and the rate constant is evaluated at $T = 500$ K. The higher level rate constant observable draws on less structure in the potential, as anticipated from the thermal averaging connecting the two observables in Fig. 1. The dominant negative response in both cases indicates that an increase in the mainly repulsive, spherically symmetric interaction can cause a corresponding decrease in the cross section and rate constant. This result could be anticipated, but the detailed form of the sensitivity and especially the interference oscillations cannot be argued intuitively. [Adapted from (13), with the permission of the *Journal of Chemical Physics*]

Fig. 3. The functional sensitivity $\delta\sigma(E)/\delta V(\mathbf{r})$ ($\text{Å}^{-1}\ \text{eV}^{-1}$) for a model system represented by a purely repulsive, spherically symmetric interaction. At a given energy E, a cut through the surface is primarily a positive function with residual quantum oscillations. At sufficiently short range, the response surface goes to zero, corresponding to the statement that the deep, classically forbidden region has a small effect on the total elastic cross section. Given the repulsive nature of the reference potential, the negative trough apparent at short range is a surprise, implying that a further increase in the potential in this region would yield a decrease in the cross section. [Adapted from (14), with the permission of *Chemical Physics*, copyright 1986]

The striking similarity of virtually all the sensitivity profiles in Fig. 4 is unexpected. Such response has been seen in a number of combustion systems, all of which are characterized by high degrees of exothermicity and nonlinear feedback in the mathematical models. Under these conditions, a type of system collapse may occur to produce what has been referred to as scaling and self-similarity relations (16). In the case corresponding to a model of the type in Fig. 4, these relations respectively take on the following form

$$\frac{\partial O_n}{\partial \alpha_j} \simeq \left(\frac{\partial O_{n'}}{\partial \alpha_j}\right)\left(\frac{\partial O_n}{\partial x}\right)\left(\frac{\partial O_{n'}}{\partial x}\right)^{-1} \tag{6}$$

$$\left(\frac{\partial O_n}{\partial \alpha_j}\right)\Big/\left(\frac{\partial O_n}{\partial \alpha_{j'}}\right) \simeq \sigma_j/\sigma_{j'} \tag{7}$$

where σ_j is a characteristic constant labeled by an index associated with the jth parameter but in fact is dependent on all of the system parameters and is approximately independent of coordinate x. Although these relations have been argued to exist under reasonable conditions, their true physical origin has yet to be fully identified. The results are tantalizing because they suggest that seemingly complex problems with highly nonlinear coupling and feedback may in fact have a much simpler dynamical response structure. The possible generality of this result may have far-ranging significance, because it directly implies an ability to systematically lump or reduce the underlying models to an essentially simpler structure (see below). With regard to the role of sensitivity analysis in revealing this behavior, it should be noted that the chemical and thermal solution profiles do not exhibit any particularly unusual behavior as a function of spatial position or temporal evolution; it is only when the system is "disturbed" and its response is monitored through the parametric sensitivities that the underlying simplicity is revealed.

Probing the relation between parameters and observable quantities is not the only systems' issues of relevance in Fig. 1. For example, the relation among the dependent variables at any given level in Fig. 1 can be quite revealing. At a particular level, the physical model and its mathematical transcription provide coupling among the system-dependent variables. In the case of chemical kinetics, for example, such coupling may be thought of as a set of intertwined relations among all of the species including reactants, intermediates, and products. The actual chemical mechanism prescribed as input provides a kinematic picture of such coupling. However, the actual chemical evolution (presumably in the laboratory as well as on the computer) can result in a highly different level of dynamic coupling.

This dynamic coupling is especially important for strongly nonlinear problems in which there may be many multiple pathways between one species and another. Therefore, it is natural to inquire, for example, about the role of a given chemical species in producing some particular product. Questions such as this, as well as their exactly analogous form in other problems including that of quantum mechanics, can be addressed by computing a special class of sensitivity coefficients referred to as Green's function elements (7)

$$G_{in}(\mathbf{r},t;\ \mathbf{r}',t') = \delta O_i(\mathbf{r},t)/\delta J_n(\mathbf{r}',t') \tag{8}$$

where $J_n(\mathbf{r}',t')$ is the flux of the nth dependent variable introduced externally at $\mathbf{r}',t'$. Therefore, the Green's function matrix element in Eq. 8 is the response of the ith dependent variable at $\mathbf{r},t$ with respect to a disturbance in the flux of the nth dependent variable at $\mathbf{r}',t'$. These quantities are referred to as Green's functions because they satisfy an inhomogeneous linearized form of the original system equation driven by a delta function source term

$$\sum_i \frac{\partial L_n}{\partial O_i}(\mathbf{r},t)\ G_{ij}(\mathbf{r},t;\mathbf{r}',t') = \delta_{nj}\,\delta(\mathbf{r}-\mathbf{r}')\,\delta(t-t') \tag{9}$$

It is also straightforward to show from Eqs. 4 and 9 that all parametric sensitivities can be directly expressed in terms of the system Green's function

$$\frac{\partial O_i}{\partial \alpha_j}(\mathbf{r},t) = -\sum_n \int d\mathbf{r}'\ dt'\ G_{in}(\mathbf{r},t;\mathbf{r}',t')\ \frac{\partial L_n}{\partial \alpha_j}(\mathbf{r}',t') \tag{10}$$

In the case of probing quantum mechanical systems, the Green's function may also be identified as just the system matrix time evolution propagator (17). A plot of a Green's function matrix associated with a carbon monoxide laminar premixed flame is shown in Fig. 5 (18). Any response found in the region $x' < x$ must be due to upstream thermal or mass diffusion.

Under the conditions associated with the presence of scaling and self-similarity response as illustrated in Fig. 4, similar behavior has also been found for the system Green's functions. Finally, if the system-dependent variables are laboratory observables such as bulk concentrations, then the Green's function matrix elements are a special class of sensitivity coefficients that may in principle be measured in the laboratory by introducing an infinitesimal flux corresponding to one variable and measuring the response of the others. This characteristic is particular to Green's function coefficients, because normal sensitivity coefficients cannot be measured in the laboratory unless the parameters correspond to control variables. However, in general, the parameter sensitivities may be related to the measurable Green's function matrix through Eq. 10. Regardless of the possibility of direct measurement, the primary value of sensitivity coefficients is for analysis and understanding of physiochemical models.

Beyond the sensitivity coefficients discussed thus far, a large variety of derived sensitivity coefficients may be generated to deal with a number of special circumstances. For example, returning again to the Green's function elements, it is possible to calculate a reduced set addressing the question of the pathway of coupling between one dependent variable and another. A large Green's function element connecting two members does not in itself elucidate the pathway by which they are connected. However, by appropriate application of system constraints, these important pathways can be elucidated. In particular, by solving the original model equations as usual with all dependent variables being present and then striking out appropriate rows and columns from the Jacobian matrix $\partial L_n/\partial O_i$, one can solve Eq. 9 for elements of the reduced Green's function matrix whose dimension is reduced exactly by the same number of removed rows and columns from the Jacobian. These latter rows and columns are labeled by the dependent

variables that are suspected of being critical linkages on the dependent variable pathways. In executing this operation, it is important to understand that the suspected linking variables are still retained in the model; however, they are constrained to their nominal values and are forbidden to respond to any disturbances in the system.

Another potentially important emerging application of sensitivity and derived sensitivity coefficients arises in the treatment of inverse problems. The sensitivity coefficients entering into Eqs. 1 and 2 address the so-called forward problem, whereby response of an output is probed with respect to a disturbance of an input. On the other hand, when a measurement is performed in the laboratory, precisely the opposite circumstance is of concern because often one desires to extract the parameters from the body of measured data. In this case, Eq. 1 may be thought of as an integral equation to be used in an inversion algorithm. Formally, this corresponds to computing the inverse sensitivity coefficients $\delta\alpha_j(\mathbf{r}',t')/\delta O_i(\mathbf{r},t)$, which provides a quantitative measure of how the ith observation projects back onto the jth system parameter. Implementing an inversion algorithm based on the sensitivities requires that considerable care be given to numerical details including stabilization (19). A related matter concerns the uniqueness of the models. This point can also be addressed by sensitivity coefficients that have the form $\delta\alpha_j(\mathbf{r}',t')/\delta\alpha_i(\mathbf{r},t)$. All of these coefficients are obtained by exchanging members of the former dependent and independent variable sets. These transformations are exactly analogous to those familiar in multivariable calculus, as routinely carried out by Legendre transformations in, for example, equilibrium thermodynamics (20).

A host of other issues and applications have been considered by the computation of specialized sensitivity coefficients. Any physically meaningful question concerning the interdependence of the dependent and independent variables of the chemical system may be addressed by appropriate sensitivity coefficients. Of course, addressing a problem does not in itself provide an answer because the resultant coefficients must be physically interpreted. In general, sensitivity information can be used to identify the significant portions of a physical model, aid in a qualitative understanding of the model, provide a quantitative assessment of the relations among all the dependent and independent variables of the system, as well as guide prioritization of new measurements for updating parameters that are suspected of having significant uncertainty.

Reduction

The sensitivity analysis methods discussed above are aimed at analyzing a physical-chemical system for its significant content. One may view this process in an iterative fashion as an effort to build up a model in complete detail. At any level in Fig. 1 (and especially in moving toward more practical applications to the right in Fig. 1), one must recognize that highly complex models become quite impractical to routinely execute even on the largest computers now available or likely to be so in the foreseeable future. A cornerstone of good physics and chemistry has been to seek the simplest model acceptable for the stated purpose. The trick is finding such models. Reduced models of complex physical and chemical problems usually result from the application of physical insight or intuition or possibly from an identification of a small parameter for series expansion. Such approaches are certainly useful, but they leave much to be desired. For example, at the molecular scale of treating intramolecular dynamics, it is reasonable to expect that physical issues associated with a local region in a molecule could be understood in terms of a reduced model with "distant" regions lumped or left out of the model. But there are currently no truly acceptable means for identifying a reduced set of atomic coordinates

and momenta to make computations practical and reliable.

One of the earliest significant efforts at treating problems of this type arose in chemical engineering, especially in connection with the desire for simplified petrochemical refining models (21). Despite the generic nature of this problem in a variety of areas, it is surprising how little attention has been paid to the development of systematic model reduction or lumping techniques. The sensitivity techniques described above directly apply and have been used as such (22). That is, one may use the magnitude of the sensitivity coefficients to identify likely parameters or dependent variables for removal to produce a simplified model. Although this technique has proved successful in a number of cases, there is still considerable room for other, more direct techniques. For example, one may seek a
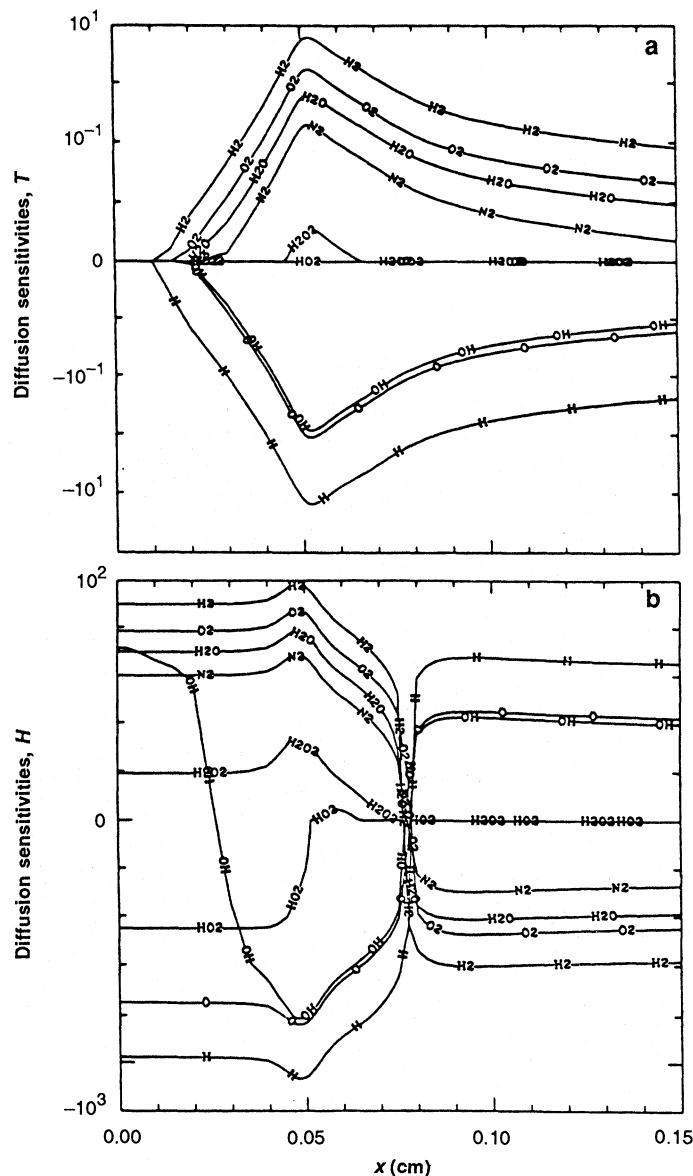

Fig. 4. Temperature (**a**) and hydrogen atom concentration (**b**) sensitivity coefficients with respect to the mass diffusion coefficients D in a hydrogen-oxygen steady, premixed laminar flame, where x is the position in the flame relative to the cold inlet at $x = 0$. The label for each curve is the diffusion coefficient of a particular species. The strong kinetic, thermal, and diffusive coupling in this system produces the strikingly evident self-similarity between the sensitivity behavior in both plots (except for that of D_{OH}). The detailed behavior of these sensitivity profiles closely follows the approximate forms in Eqs. 6 and 7. [Adapted from (15), with the permission of *Combustion Science and Technology*, copyright 1988]
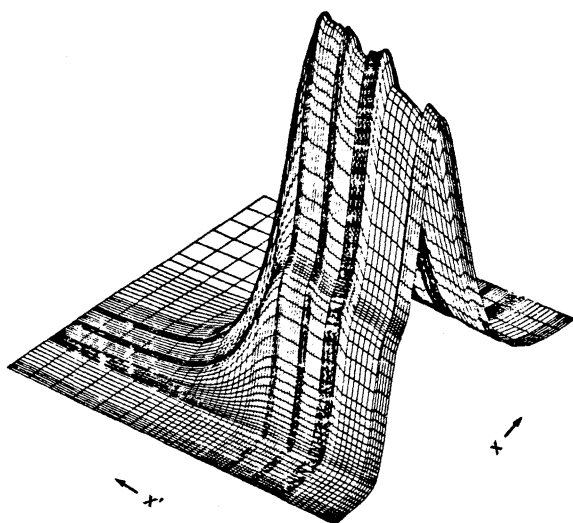
Fig. 5. Sensitivity of carbon dioxide with respect to a disturbance of the flux of hydrogen $G_{CO_2,H_2}(x,x')$. This case corresponds to a steady, premixed laminar one-dimensional carbon monoxide flame model, where the presence of diffusion is clearly indicated by the response of carbon dioxide at position x upstream, $x < x'$ in the flow.

projective-type transformation $O' = MO$ in which the original n-vector of dependent variables O has been projected onto the vector O' of dimension n', where $n' < n$ and M is a nonsquare lumping matrix of corresponding dimensions (23). Thus far, work along these lines has largely been confined to treating problems of reactive flow and particularly identifying the necessary and sufficient conditions for exact lumping to be present. Realistic problems are not likely to be amenable to exact lumping, but identification of such criteria can provide a benchmark and algorithmic guide to seeking approximate lumping techniques. Although some advances have been made and practical results achieved, this relatively undeveloped area deserves further attention.

Concluding Remarks

Serious mathematical modeling of chemical or other systems requires knowledge of the important variables and consequences of uncertainties in the particular model. However, at least until recently in the area of physiochemical system model development, this matter has not received major attention. It is certainly necessary to first have the ability to solve the model equations, and the apparent lack of attention mentioned above is probably due in part to an ongoing preoccupation with just getting "an answer." Sensitivity analysis does not come without extra cost, but, depending on how the model equations are solved, this cost can often be reduced to a reasonable level, as shown by the increasing number of illustrations in the literature. Indeed, if one can afford to perform the modeling, then the modeling alone should not be viewed as complete without a systems analysis. All too often, modeling stops at the point when the results "agree" with available experimental data. Data are never complete, and such premature truncations of effort can often miss the essential goal of a deep physical understanding of the system. Some workers have gone so far as to state that theoretical methods are now sufficiently advanced that it is intellectually dishonest to perform modeling without sensitivity analysis (24).

Although sensitivity analysis forms the cornerstone of molecular systems analysis as it stands, the subject is emerging and may well take on other forms. For example, sensitivity analysis in its gradient-based form is inherently local and deals with the response or

performance of a system at a particular operating point in parameter space. Ultimate questions of sensitivity and systems analysis of all types are embodied in the global structure of the parameter space. A full knowledge of the space would imply all knowledge about the system, and this will never be achieved nor is it desirable. Nevertheless, a more global perspective would be most valuable and efforts along these lines in chemical systems go back a number of years (5, 6). More recently, a new approach based on Lie group techniques has been pursued (25).

In general, molecular systems analysis is not just a technique but rather a way of thinking about and treating physiochemical problems. This mode of operation has guided the latest developments of molecular-scale systems analysis in the area of optimal control of molecular motion (26). The generic mathematical structure of systems analysis suggests that a breakthrough in treating systems questions in any one physical problem will have immediate applications to others, which would make the effort extremely worthwhile and rewarding. In deciding to pursue molecular-scale systems analysis, an important question is: What can one expect from the investment of the additional time and cost? This question needs to be answered while keeping in mind that modeling will continue to be performed regardless of the incorporation of systems techniques. Computational modeling alone, notwithstanding its successes and considerable recent attention, has severe limitations. Quite simply, systems tools provide a means for extracting maximum benefit from such modeling efforts. Finally, there is also the question of what one may expect from a joining of modeling and systems analysis with experimental endeavors. There is a danger in overselling the capabilities of the current modeling-analysis tools, but it is reasonable to suggest that with these tools one should be able to short-circuit the traditional mix and try laboratory methods. This comment may be especially appropriate for materials design, where modeling is increasingly being used but systems techniques have yet to be used.

REFERENCES AND NOTES

1. H. Rabitz et al., Annu. Rev. Phys. Chem. **34**, 419 (1983); J. Tilden et al., in Modelling of Chemical Reaction Systems, K. Ebert, P. Deuflhard, W. Jager, Eds. (Springer-Verlag, Berlin, 1981), pp. 69–91; H. Rabitz, Physica **20D**, 67 (1986).
2. R. Cannon, Jr., Dynamics of Physical Systems (McGraw-Hill, New York, 1967); H. Martens and D. Allen, Introduction to Systems Theory (Merrill, Columbus, OH, 1969).
3. R. Tomovick and M. Vukobratovic, General Sensitivity Theory (American Elsevier, New York, 1972).
4. J. Eberhardt, P. Hay, J. Carpenter, Mater. Res. Soc. Symp. Proc. **63**, 191 (1986).
5. R. Iman, H. I. Helton, J. Campbell, J. Qual. Technol. **13**, 174 (1984); ibid., p. 232.
6. R. Cukier, H. Levine, K. Schuler, J. Comput. Phys. **26**, 1 (1978).
7. H. Rabitz, in The Mathematics of Combustion, J. Buckmaster, Ed. (Society for Industrial and Applied Mathematics, Philadelphia, 1985), pp. 47–95; Chem. Rev. **87**, 101 (1987).
8. Y. Reuven, M. Smooke, H. Rabitz, J. Comput. Phys. **64**, 27 (1986).
9. R. Judson, S. Shi, H. Rabitz, J. Chem. Phys. **90**, 2283 (1989).
10. S. Shi and H. Rabitz, ibid. **86**, 6190 (1987).
11. T.-S. Ho and H. Rabitz, Phys. Rev. **37**, 4184 (1988).
12. T. Thacher and H. Rabitz, unpublished results.
13. M. Smith, S. Shi, H. Rabitz, J. Chem. Phys., in press.
14. R. Guzman and H. Rabitz, Chem. Phys. **109**, 85 (1986).
15. M. Smooke et al., Combust. Sci. Technol. **295**, 59 (1988).
16. H. Rabitz and M. Smooke, J. Phys. Chem. **92**, 1110 (1988).
17. See, for example, L. Schiff, Quantum Mechanics (McGraw-Hill, New York, 1968).
18. M. Mishra, R. Yetter, Y. Reuven, M. Smooke, H. Rabitz, in preparation.
19. T.-S. Ho and H. Rabitz, J. Chem. Phys. **89**, 5614 (1988).
20. See, for example, N. Gokcen, Thermodynamics (Techscience Incorporated, Hawthorne, CA, 1975).
21. S. Jacob et al., Am. Inst. Chem. Educ. J. **22**, 701 (1976).
22. R. Yetter, F. Dryer, H. Rabitz, Combust. Flame **59**, 107 (1985).
23. G. Li, Chem. Eng. Sci. **31**, 1261 (1984); _____ and H. Rabitz, ibid. **44**, 1413 (1989).
24. C. Kolb, private communication.
25. C. Wulfman and H. Rabitz, J. Phys. Chem. **90**, 2264 (1986).
26. A. Peirce, M. Dahleh, H. Rabitz, Phys. Rev. A **37**, 4950 (1988); S. Shi, A. Woody, H. Rabitz, J. Chem. Phys. **88**, 6870 (1988).
27. The author's research on molecular systems analysis over the past several years has been supported by the Department of Energy, the Office of Naval Research, and the Air Force Office of Scientific Research.