CHEMICAL REVIEWS

REVIEW

pubs.acs.org/CR

Update 1 of: Sensitivity Analysis for Chemical Models

Andrea Saltelli,* Marco Ratto, Stefano Tarantola, and Francesca Campolongo

European Commission, Joint Research Centre of Ispra (I), Institute for the Protection and Security of the Citizen, TP 361, Via Enrico Fermi 2749, 21027 Ispra (VA), Italy

CONTENTS

1. INTRODUCTION

Chemists routinely create models of reaction systems to understand reaction mechanisms, kinetic properties, process yields under various operating conditions, or the impact of chemicals on ~~man~~humans and the environment. As opposed to concise physical laws, these models are attempts to mimic the system by hypothesizing, extracting, and encoding system features (e.g., a potentially relevant reaction pathway), within a process that can hardly be formalized scientifically.[1] A model will hopefully help to corroborate or falsify a given description of reality, e.g., by validating a reaction scheme for a photochemical process in the atmosphere, and possibly to influence reality, e.g., by allowing the identification of optimal operating conditions for an industrial process or suggesting mitigating strategies for an undesired environmental impact.

These models are ~~customarily~~ built in the presence of uncertainties of various levels, in the pathway, in the order of the kinetics associated to the pathway, in the numerical value of the kinetic and thermodynamic constants for that pathway, and so on.

Propagating via the model all these uncertainties onto the model output of interest, e.g., the yield of a process, is the job of uncertainty analysis. Determining the strength of the relation between a given uncertain input and the output is the job of sensitivity analysis.[2,2a]

A straightforward implementation of the "sensitivity" concept is provided by model output derivatives. If the model output of interest is Y, its sensitivity to an input factor X_i is simply $Y'_{Xi} = \partial Y/\partial X_i$. This measure tells how sensitive the output is to a perturbation of the input. For discrete input factors, local sensitivities might be impossible to evaluate as wide perturbations of the input would be implied. If a measure independent from the units used for Y and X_i is needed, $S^r_{Xi} = (X^0_i/Y^0)(\partial Y/\partial X_i)$, which denotes the so-called elasticity coefficient, can be used, where X^0_i is the nominal value of factor X_i and Y^0 is the value taken by Y when all input factors are at their nominal value. The nominal (or reference, or design) value X^0_i can be the mean (or median) value when an uncertainty distribution (either empirical or hypothesized) is available. In this latter case an alternative measure is $S^\sigma_{Xi} = (\sigma_{Xi}/\sigma_Y)(\partial Y/\partial X_i)$, where the standard deviations σ_{Xi}, σ_Y are uncertainty analysis' input and output, respectively, in the sense that σ_{Xi} comes from the available knowledge on X_i, while σ_Y must be inferred using the model.

Wheras S^r_{Xi} is a dimensionless version of the pure derivative $(\partial Y/\partial X_i)$ and, hence, still a purely local measure (i.e., relative to the point where the derivative is taken), S^σ_{Xi} depends upon the uncertain range of factor X_i, and is in this sense a more informative measure. *Coeteris paribus*, factors with larger standard deviations, have more chance to contribute significantly to the uncertainty in the output.

Local, derivative-based sensitivity measures can be efficiently computed by an array of techniques, ranging from automated differentiation (where the computer program that implements the model is modified so that the sensitivities are computed with a modicum of extra execution time[3,3a]) to direct methods (where the differential equations describing the model are solved directly in terms of species concentrations and their derivatives[4]). There is a vast amount of literature on these sensitivity measures.[5−10,11] The majority of sensitivity analyses met with in chemistry and physics are local and derivative-based. Local sensitivities are useful for a variety of applications, such as the solution of inverse problems, e.g., relating macroscopic observables of a system, such as kinetic constants, to the quantum mechanics properties of the system,[6] or the analysis of runaway and parametric sensitivity of various types of chemical reactors.[8] Contexts where local sensitivity has been widely used are as follows: (1) to understand the reaction path, mechanism, or rate-determining steps in a detailed

Received: August 22, 2011
Published: May 1, 2012

dx.doi.org/10.1021/cr200301u | *Chem. Rev.* 2012, 112, PR1–PR21

kinetic model with a large number of elementary reactions, e.g., in photochemistry or in combustion chemistry,[4,7,9] (see ref 12 for an alternative approach in this context), (2) to extract important elementary reactions from a complex kinetic model to obtain a reduced model (e.g., a minimal reaction scheme) with equivalent predictive power[7] or to select important reactions for further analysis,[13,14] (3) to estimate the output of a computer program in the neighborhood of a given set of boundary conditions (BCs) without rerunning the program [This is often the rationale for using automated differentiation software.[3,15] This approach may be effective for deviations of up to 10−20% away from the baseline BC.], and, (4) for variational data assimilation, to reconcile model predictions with observations.[6,16,17]

In these local sensitivity measures the effect of X_i is observed while assuming all other factors fixed. This approach falls, hence, in the class of the one-factor-at-a-time (OAT) methods. A nonlocal OAT approach, often met in the literature, makes use of incremental ratios taken by moving factors one at a time away from their baseline value by a fixed (e.g., 5%) fraction, irrespective of the factor's presumed uncertainty range.[18]

Using derivative or otherwise OAT methods for the purpose of assessing the relative importance of input factors, e.g., to decide which factor mostly deserves better measurements, can only be effective if the model is linear in all its factors, unless some form of averaging of the system derivatives over the space of the input factors is performed.[18a,b] The same reservation holds if the purpose of the sensitivity analysis is to screen the factors as to fix those which are less influential on the output~~although when the factors' derivatives differ by orders of magnitudes from one another, their use in screening might be safe enough~~. In general a single measure such as $S^{\sigma}_{Xi} = (\sigma_{Xi}/\sigma_Y)(\partial Y/\partial X_i)$ can take care of the fact that different factors have different ranges of uncertainty but not of model nonlinearities due to the same factors.

Second-order derivatives can improve the sensitivity analysis offered by the first-order methods[14,19] and are useful for variational data assimilation.[16]

Additional software sources for local methods are given in ref 3. Among these, we would like to recommend as a suggested practice the KINALC package.[92] KINALC is a postprocessor to CHEMKIN, a widespread simulation program, and carries out processing sensitivity analysis including principal component analysis of the sensitivity matrix. As argued in ref 7, a principal component analysis (PCA − a multivariate statistics technique) is a useful postprocessing tool to local sensitivity analysis when the output is not a scalar but a vector of, e.g., species concentrations. PCA can extract at no additional cost relevant features of the chemical mechanism and can assist in the setup of the parameter estimation step.

In the 1970s chemists[20−23] applied Fourier transforms to sensitivity analysis. Their motivation was the realization that most models met in chemistry are of a rather nonlinear nature. Nonmonotonic, nonadditive features, to which we shall return later in this review, are also ~~not un~~common. For these models, OAT methods can be of limited use if not outright misleading when the analysis aims to assess the relative importance of uncertain factors. OAT methods do not identify interactions among factors and are extremely poor at exploring multidimensional factors spaces, as one can ascertain with elementary geometric considerations.[16a] A good sensitivity measure should be model-free, i.e., independent from assumptions about the model linearity or additivity. To this effect, Cukier, Schaibly, and co-workers developed the Fourier amplitude sensitivity test (FAST),[20−23] ~~defined as the Walsh amplitude sensitivity procedure (WASP)~~ later made computationally available by Koda, McRae, and others.[25,26] ~~variant~~ For discrete input factors, despite the possibility to transform them into continuous uniform distributions over a unit interval, FAST is an approximate method. A reformulation of the analysis has been proposed by Pierce and Cukier[24] using Hadamard ordered Walsh functions, obtaining exact expressions for the sensitivity measures of ~~discrete~~ input factors that are intrinsically two-valued.

What FAST does, in a nutshell, is to explore the hyperspace of the input factors with a periodic curve (trajectory) built using a different frequency for each factor. This can then be used to decompose the variance $V = \sigma_Y^2$ of Y using spectral analysis, so that $V = V_1 + V_2 + ... + V_k + R$, where V_i is that part of the variance of Y that can be attributed to X_i alone, k is the number of uncertain factors, and R is a residual. Thus, $S_i = V_i/V$ can be taken as a measure of the sensitivity of Y with respect to X_i. We will offer a precise definition of V_i and R in section 2.

Although FAST is a sound approach to the problem, it has seen moderate use in the scientific community at large, including among chemists, and few applications of FAST are available in the literature.[27−30] Further chemical applications of FAST are cited in ref 4. At the time of its development, FAST was laborious to implement and computationally expensive. Some researchers were uncomfortable with moving away from the mathematical appeal of derivatives[~~The review System Analysis at Molecular Scale by H. Rabitzstates, "Generally the emphasis in sensitivity analysis is not on the explicit introduction of any particular variation [in the input] but rather on the computation and examination of the sensitivity coefficients [the derivatives], as they are independent of any special variation in the parameters". The same author later contributed considerably to the development of global sensitivity analysis by introducing a new class of high-dimensional model representation (section 2).~~]. For these reasons FAST is mentioned in some reviews of sensitivity analysis methods[4,7,8,31−35] but ignored in others.[10,36] Renewed interest in FAST has been associated to the use of random balanced design for variance decompositions; see ref 36a for a review.

In the 1990s, several investigators, sometimes without realizing it, developed Monte Carlo-based estimates of the FAST sensitivity measure; see refs 37−44. In these approaches, the space of the input factors was explored using Monte Carlo-based techniques (such as Latin hypercube, pseudorandom or quasi-random sampling), rather than by the Fourier trajectories, but in general the same sensitivity measure $S_i = V_i/V$ was computed.[52] The best formalization of this approach is due to Sobol'.[42]

At the same time, practitioners in risk analysis were using for the purpose of sensitivity analysis various kinds of Monte Carlo (MC)-based linear regression.[31] In these approaches, the space of the input factors was sampled via the Monte Carlo method and a linear regression model was built (e.g., by a least-squares calculation) from the values of Y produced by the model.

~~We anticipate here that~~The standardized regression coefficients β_i thus generated, where $\beta_i = (\sigma_{Xi}/\sigma_Y)b_i$ and b_i is the estimate of the regression coefficient, are related to the FAST measure, as well as to S^{σ}_{Xi}. In fact, for linear models $\beta_i^2 = S_i = (S^{\sigma}_{Xi})^2$. In ref 45 we compare different sensitivity measures with respect to their effectiveness in apportioning the variance in the output to different inputs. In this sense S^{σ}_{Xi} is an effective measure for linear models, β_i is an effective measure for moderately nonlinear models, for which an effective linear regression model can be built, and S_i is the model-free extension that works even for strongly

dx.doi.org/10.1021/cr200301u |Chem. Rev. 2012, 112, PR1–PR21

nonlinear models and nonmonotonic relationships between input and output.

Rabitz and co-workers[46,47] developed alternative strategies for global sensitivity analysis that are inspired by the work of Sobol', and, hence, homologous to FAST, but are based on decomposing the model output of interest on the basis of finite differences built along lines, planes, and hyperplanes that pass through a given selected point in the space of the input factors. Rabitz's approach can be seen as "in between" derivative-based methods and global methods, such as, e.g., those based on Monte Carlo and/or meta-modeling.~~can also be used to compute the variance-based sensitivity indices S_i.~~

A class of global methods of interest is that of the variance-based measures. These aim to apportion the variance of the output of interest into bits due to factors and their combinations. The latest scientific production of Rabitz and co-workers in sensitivity analysis has focused on Monte Carlo-based estimates of variance-based indices, see, e.g., ref 47a and 47b, bringing this line of research into the mainstream of meta-modeling-based sensitivity analysis described in section 2.10.

Finally, it is important to note that using variance-based techniques in numerical experiments is the same as applying ANOVA [analysis of variance[33,48] (~~here and in the following we shall list references in chronological order~~)] in experimental design, as the same variance decomposition scheme holds in the two cases. One could hence say that modelers have converged with experimentalists treating Y, the outcome of a numerical experiment, as an experimental outcome whose relation to the control variables, the input factors, can be assessed on the basis of statistical inference. Sacks, Welch, and others[49,50] were among the first to think along these lines.~~Morris developed an effective experimental design scheme for numerical experiments which has similarities to a variance-based measure.~~

Today the Bayesian community has developed a school of model experimentation via Gaussian emulators. which sees itself as the heir of these investigators.[50a−c] More in general, meta-modeling-based sensitivity analysis has strongly developed in a number of promising directions, since Blanning's and Kleijnen's seminal ideas:[50d,e] kriging[69] (of which Gaussian process modeling is its most common variant), nonparametric regressions,[70,70a,70b] polynomial chaos expansions,[71,72] and others.

This convergence of FAST-based and sampling-based strategies for sensitivity analysis and also a convergence between these and experimental design theory, which escaped earlier reviews,[8] vindicate the original intuition of the FAST developers that S_i was a good measure for chemical models. Both FAST and MC computation schemes have been upgraded in recent years,[2a,45,65c] becoming less expensive and easier to apply, as we shall see in the next sections. A further element of convergence can be seen in screening methods for sensitivity analysis, which also have important similarities to a variance-based measure.[51,51a]

As already mentioned, OAT approaches still dominate the chemical literature[16a] even when the purpose of the analysis is to assess the relative importance of input factors in the presence of factors uncertainty.

To contrast this poor practice, we shall select and review those which we consider as the most promising modern approaches to sensitivity analysis, with emphasis on ~~methods in the FAST family~~ variance-based methods, comparing, with the help of worked examples, the performances of these with different kinds of local, regression, meta-modeling, or screening-based measures.

The literature (see, e.g., refs 2, 61, 64a, 70a, 93−96, and 103) offers more methods for sensitivity analysis than are reported in the present review. Some of these methods are domain-specific, such as, for instance, methods for use in reliability engineering;[97] others require a direct intervention of the analyst on the model (such as automated differentiation). We have privileged general methods that treat the model as a black box and that are not too laborious to implement. A few computational recipes are also offered for the reader.

2. METHODS

2.1. A Simple Example, Using Local Sensitivity Analysis

It would be impossible to describe all sensitivity analysis methods within the purpose of the present work. Available reviews are refs 4−8, 10, 11, 16a, 18, 31, 34−36, and 55−57. Those of Rabitz,[5,6] Turányi and Tomlin,[4,7] and Varma and Morbidelli[8] are of particular interest for chemists. References 31 and 34 cover well Monte Carlo-based regression methods, ref 10 focuses on local strategies, and ref 56 focuses on experimental design methods.

A wide spectrum of different perspectives and approaches can be found in ref 2, a multiauthor book with input from practitioners such as Rabitz, Turányi, Helton, Sobol', the authors of the present review, and others. A primer for beginners is ref 2a. Our plan here is to offer a selection of sensitivity analysis methods, with emphasis on global methods, which might be of relevance to and applicable by the *Chemical Reviews* readership. The methods are illustrated by examples. We start with a simple reversible chemical reaction A ↔ B, with reaction rates k_1 and k_{-1} for the direct and inverse reactions, respectively, whose solution, for the initial conditions (ICs)

$$\begin{aligned}[A](t=0) &= [A]_0\\ [B](t=0) &= 0\end{aligned} \tag{1}$$

is

$$[A] = \frac{[A]_0}{k_1 + k_{-1}}(k_1 e^{-(k_1 + k_{-1})t} + k_{-1}),$$
$$[B] = [A]_0 - [A] \tag{2}$$

Figure 1 gives the time evolution of the concentrations of species A and B. This model is so simple as to allow a characterization of the system sensitivity by analytic methods, but we shall work it out as if it were a system of partial differential equations for a large reaction model, as tackled by chemists using solvers such as FACSIMILE,[58] CHEMKIN,[59] or others, where the relative effect of the uncertain inputs in determining the uncertainty of the output of interest is unknown. We assume that the reaction rates are uncertain and are described by continuous random variables with known probability density functions (pdf's) that characterize their uncertainty.

$$\begin{aligned}k_1 &\sim N(3, 0.3)\\ k_{-1} &\sim N(3, 1)\end{aligned} \tag{3}$$

where the symbol ∼ stands for "distributed as" and N stands for normal distribution. Thus, both uncertain factors are normally distributed with mean 3. The standard deviation is 0.3 for k_1 and

dx.doi.org/10.1021/cr200301u |*Chem. Rev.* 2012, 112, PR1–PR21

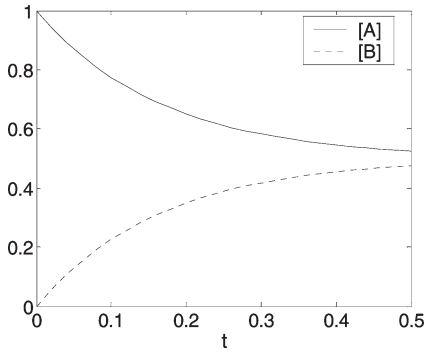


Figure 1. Time evolution of [A] and [B] from eq 2.

1 for k_{-1}. Figure 2 gives the absolute values of the derivative-based sensitivities, i.e.:

$$[A]'_{k_1} = \frac{\partial[A]}{\partial k_1}, \quad [A]'_{k_{-1}} = \frac{\partial[A]}{\partial k_{-1}} \tag{4}$$

computed at the nominal value $k_1 = k_{-1} = 3$, as well as the absolute values of the S^σ sensitivities:

$$S^\sigma_{k_1} = \frac{\sigma_{k_1}}{\sigma_{[A]}}\frac{\partial[A]}{\partial k_1}, \quad S^\sigma_{k_{-1}} = \frac{\sigma_{k_{-1}}}{\sigma_{[A]}}\frac{\partial[A]}{\partial k_{-1}} \tag{5}$$

The value of $\sigma_{[A]}$ used in Figure 2 is not the exact one but has been computed using the approximation ~~$\sigma^2_Y \approx \sum_{i=1}^{k} \sigma^2_{X_i}(\partial Y/\partial X_i)^2$ to model $Y = f(X_1,X_2,...,X_k)$, which for our simple two-factor model of eq gives~~

$$\sigma^2_{[A]} \cong \sigma^2_{k_1}\left(\frac{\partial[A]}{\partial k_1}\right)^2 + \sigma^2_{k_{-1}}\left(\frac{\partial[A]}{\partial k_{-1}}\right)^2 \tag{6}$$

(identity only holds for linear models) or equivalently:

$$(S^\sigma_{k_1})^2 + (S^\sigma_{k_{-1}})^2 \cong 1 \tag{7}$$

We discuss the applicability of this approximation in a moment. It is evident from Figure 2 that $S^\sigma{}_{k_1}$ and $S^\sigma{}_{k_{-1}}$ offer a more realistic picture of the relative importance of k_1 and k_{-1} in determining the uncertainty of [A] than $[A]'_{k_1}$ and $[A]'_{k_{-1}}$, as the sigma-normalized sensitivity measures are capable of weighting the larger role of k_{-1}, which descends from its larger standard deviation (one expects that more uncertain factors propagate more uncertainty into the output). This is not to say that $[A]'_{k_1}$ and $[A]'_{k_{-1}}$ are useless. We have used them, for instance, to compute an approximate map of [A] as a function of k_1 and k_{-1} using a simple Taylor expansion (see Figure 3). This kind of approximation[60] becomes very valuable when the model under analysis is expensive to run. [Throughout this work, computation cost must be understood as the number of times one needs to run the model that computes $Y = f(X_1,X_2,...,X_k)$. The time needed to compute the sensitivity statistics (e.g., S^σ, S_i, ...) is usually negligible in comparison.] More accurate tools for this kind of model approximation, also shown in Figure 3, are discussed in section 2.5. Note that the entire Taylor representation in Figure 3 was built using for each plot just the function value at $k_1 = k_{-1} = 3$ plus the two derivatives $[A]'_{k_1}$ and $[A]'_{k_{-1}}$ at the same point.

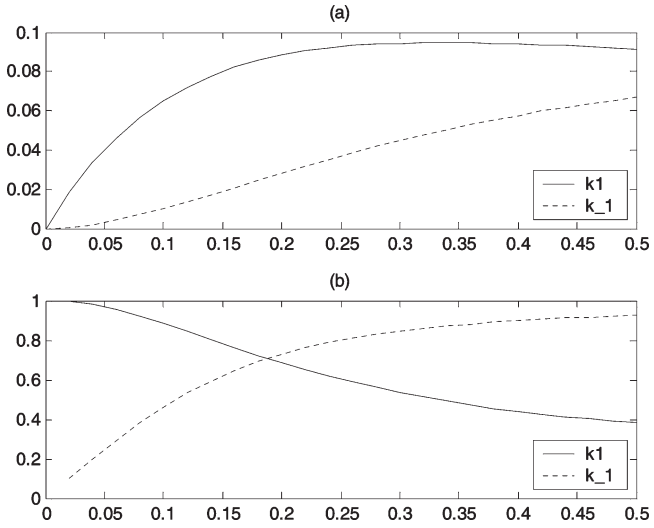


Figure 2. Absolute values of (a) $[A]'_{k_1} = \partial[A]/\partial k_1$ and $[A]'_{k_{-1}} = \partial[A]/\partial k_{-1}$ and (b) $S^\sigma_{k_1} = (\sigma_{k_1}/\sigma_{[A]})(\partial[A]/\partial k_1)$ and $S^\sigma_{k_{-1}} = (\sigma_{k_{-1}}/\sigma_{[A]})(\partial[A]/\partial k_{-1})$ as a function of time.

Derivative-based measures such as $\partial[A]/\partial k_1$ and $S^\sigma{}_{k_1}$ are members of a large class of local measures used in chemistry, which includes, e.g., functional sensitivities and feature sensitivities.[3,4−10,11] ~~These are extensively dealt with in the literature.~~ Methods to compute these derivatives for large systems of differential equations include the Green functions method, the direct method, the decoupled direct method, the adjoint method, and others.[7,8,11] Increasing use of automatic differentiation techniques is made in chemistry whereby pieces of code are automatically generated from the existing computer model code for the evaluation of derivatives of the type $\partial[A]/\partial k_1$ (automatic differentiation tools are, for example, ADIFOR, ADIC, and ADOL-C).[3,3a] Given that the emphasis of the present review is on global methods, we will not describe them here. ~~Automated differentiation methods, whereby the modeler modifies the simulation model so that it can compute derivatives with a minimum of extra computing time, are also extensively used in chemistry.~~

The $S^\sigma{}_{k_1}$ and $S^\sigma{}_{k_{-1}}$ curves in Figure 2b are an example of quantitative, albeit approximate, sensitivity analysis. Imagine that k_1 and k_{-1} are two poorly known rates of a more complex system and that we need to know which of them—once properly determined in the laboratory—would give us better chances to reduce the uncertainty in the output [A] of interest. Figure 2b would allow us to say that, if we need to reduce the uncertainty of [A] at the beginning of the process ($t = 0.05$), then k_1 is a better candidate than k_{-1}. The reverse is true if we are interested in [A] near equilibrium ($t = 0.4$, when concentrations nearly stabilize; see Figure 1). Considerations of this nature are also relevant for the purpose of model calibration (see section 2.6). The reader will believe Figure 2 conditionally upon the applicability of approximation eq 7, which tells us that the variance of [A] can be partitioned in bits proportional to the squared $S^\sigma{}_{k_1}$ and $S^\sigma{}_{k_{-1}}$. We reconsider the validity of this approximation in the next section.

2.2. Monte Carlo Methods on the Simple Example

We move now into Monte Carlo simulation, drawing independent samples from the distributions of k_1,k_{-1} (eq 2) and running the computer program that evaluates the solutions to eq 2.

dx.doi.org/10.1021/cr200301u |*Chem. Rev.* 2012, 112, PR1–PR21

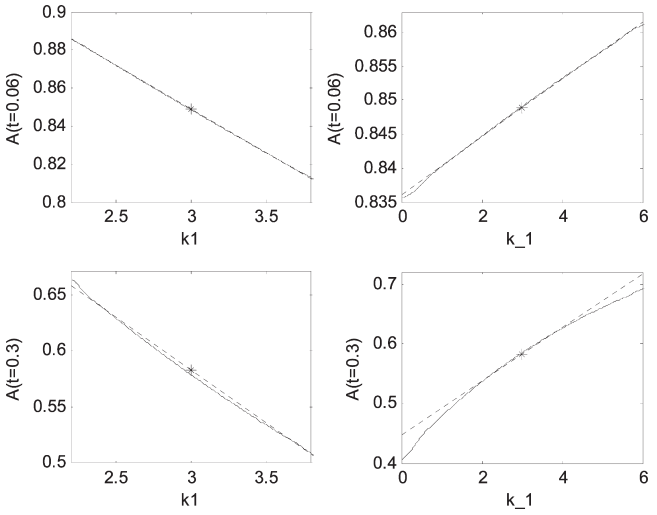


Figure 3. First-order Taylor expansion (dotted straight lines) and first-order ANOVA-HDMR decomposition f_{k_1}, $f_{k_{-1}}$ (solid black lines). The star represents the base value, at which the Taylor expansion is constructed.

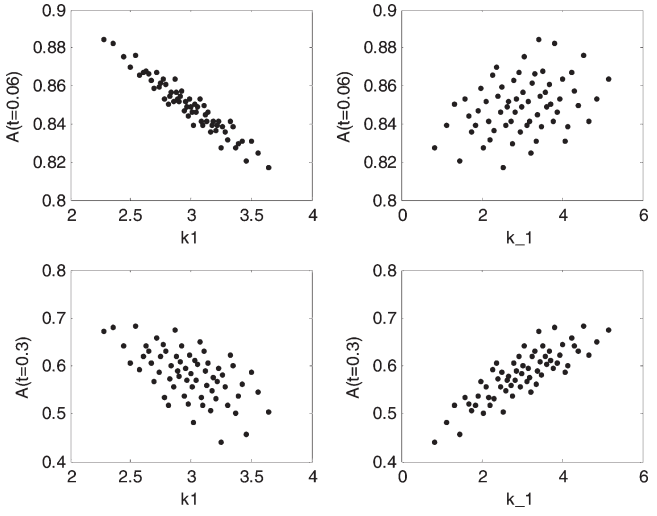


Figure 4. Scatter plots of [A] versus k_1,k_{-1} at time $t = 0.06$ and $t = 0.3$. k_1 appears more influential than k_{-1} at $t = 0.06$, while the reverse is true at $t = 0.3$.

This would be a slow step if eq 2 were a large system of partial differential equations to be solved numerically. Imagine we run eq 2 just 64 times (this number is chosen arbitrarily; a practical guide for choosing the sample size of a computer experiment is available[11a]), obtaining 64 different estimates $[A]_i$, with $i = 1, 2, ..., 64$, each corresponding to a sample k_{1i}, k_{-1i}, where the two factors have been drawn independently from one another but in such a way that each of them is a sample from its distribution (eq 2).

One way to use these estimates in sensitivity analysis is to make scatter plots (see Figure 4; scatter-plots at time $t = 0.3$ and $t = 0.6$) which allow a visual impression of the input−output relationship, including, e.g., the degree of linearity and monotonicity, or the existence of modes.[31,61] For mathematical models with tens of uncertain factors, scatter plots become impractical, and a more concise description of the model sensitivities can be obtained by feeding $[A]_i$, k_{1i}, and k_{-1i} into a regression algorithm, searching for a linear model of the form

$$[A] = b_0 + b_1 k_1 + b_{-1} k_{-1} \tag{8}$$

The b_i coefficients are dimensioned, and in order to make the coefficients comparable they are standardized to obtain

$$[\tilde{A}] = \beta_1 \tilde{k}_1 + \beta_{-1} \tilde{k}_{-1} \tag{9}$$

where $[\tilde{A}] = ([A] - \mu_{[A]})/\sigma_{[A]}$ and $\tilde{k}_i = (k_i - \mu_{ki})/\sigma_{ki}$ are standardized variables, $\mu_{[A]}$ and μ_{ki} are the means of [A] and k_i, respectively, $\sigma_{[A]}$ and σ_{ki} are the standard deviations, $\beta_i = (\sigma_{[A]}/\sigma_{ki})b_i$ are the so-called standardized regression coefficients (SRCs), and we have used k_i to indicate either k_1 or k_{-1}. It is a known result of linear regression analysis[62] that, if the factors are independent and the model is linear, then for the model in eq 2:

$$\beta_1^2 + \beta_{-1}^2 = 1 \tag{10}$$

If the model, as in our case, deviates from linearity, then the sum of the squared β's will quantify the deviation. More often, this statistics is computed directly from the simulation data and the regression model results:

$$R^2_{[A]} = \sum_{i=1}^{N} \frac{([A]^*_i - \mu_{[A]})^2}{([A]_i - \mu_{[A]})^2} \tag{11}$$

where N is the number of simulations, 64 in this case, $[A]_i$ are the simulation results, and $[A]^*_i$ are the values of [A] provided by the regression model (eq 8). $R^2_{[A]}$, known as the model coefficient of determination, is a positive number in [0,1] which indicates ~~which~~ the fraction of the original model variance ~~is~~ explained by the regression model. When this number is high, e.g., 0.7 or higher, then we can use the standardized regression coefficients for sensitivity analysis, albeit at the price of remaining ignorant about that fraction of the model variance not explained by the SRCs. An application of this strategy to a kinetic model (KIM) for tropospheric oxidation of dimethyl sulfide (DMS) is in ref 63, where a rather high value of R^2 allowed factors to be ranked confidently in a system with about 50 temperature-dependent chemical reactions.

Note that an improvement of the performance of the regression-based approach, i.e., a higher value of R^2_Y, can be obtained by transforming both the input and the output sample vectors to ranks, e.g., rank N for the highest Y and rank 1 for the lowest, and the same for the input factors.[64,64a] Rank transformation can substantially linearize a nonlinear, albeit monotonic, function. The problem with this approach is that the conclusions of the sensitivity analysis apply to the rank version of the model rather than to the model itself.[65]

The identity $\beta^2_{k\pm1} = (S^{\sigma}_{k\pm1})^2$ for a linear model is evident (eqs 7 and 10). Yet, when the model is even partially nonlinear, the standardized regression coefficients are superior to the normalized derivatives, first, because they allow the degree of nonlinearity of the model to be estimated and, second, as they offer a measure of the effect of, e.g., k_1 on [A] which is averaged over a sample of possible values for k_{-1}, as opposed

dx.doi.org/10.1021/cr200301u |Chem. Rev. 2012, 112, PR1–PR21

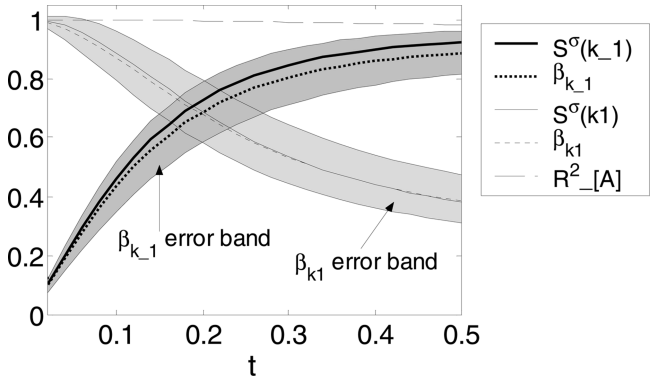


Figure 5. (i) $R^2_{[A]}$ versus time; (ii) $S^{\sigma}_{k_1}$ and β_{k_1} with confidence bounds versus time (descending lines); (iii) $S^{\sigma}_{k_{-1}}$ and $\beta_{k_{-1}}$ with confidence bounds versus time (ascending lines). Error bounds are based on 100 bootstrap replicas of the 64 original data points.

to being computed at the fixed point $k_{-1} = 3$, as was the case for S^{σ}_{ki}.

In Figure 5 we have plotted the S^{σ}_{ki} and β_{ki} for both k_1 and k_{-1}. We see that for this test model (eq 2) the two measures are equivalent. The model coefficient of determination for these data is very high and ranges from $R^2_{[A]} = 1$ at the initial time point to $R^2_{[A]} = 0.98$. To stay with our pretension that the model in eq 2 is something expensive to estimate, we have performed only 64 model evaluations, and we have, hence, computed the error bounds (2 standard deviations) on the β_i's using bootstrap;[65a] i.e., we have reestimated the regression (eq 8) by drawing 100 different samples (with replacement) of size 64 of the original 64 simulations. This procedure helps us to decide whether N should be increased beyond the present value of 64, e.g., when the uncertainty bounds are too wide for our purposes.

On the basis of the value of $R^2_{[A]}$ and on the basis of Figure 5, we can say that the exploration of the space of the input factors k_i's used in the computation of the β_{k_i}'s does not make much of a difference, so that eq 7 (based on a single point in that space) is a valid approximation for this model. Yet what would happen if we had a model with a low R^2_Y? Obtaining a measure of the average local sensitivity, e.g., $<\partial[X]/\partial k_i>$, the effect of kinetic rate k_i over the concentration of species X averaged over all the space of the uncertain input k's, was the main motivation of Cukier and co-workers in the 1970s to develop a new method, the Fourier amplitude sensitivity test (FAST), suited to nonlinear problems.

~~Before moving into a discussion of it, let us make the point of the preceding discussion.~~ In summary, derivatives can provide detailed information about system behavior. Yet, usual practice to estimate them at a single point in the space of the input limits their applicability away from that point, which is something needed in sensitivity analysis when there are ~~sensible~~ considerable uncertainties in the input factors. In ref 16a it is shown that the use of the central or baseline point for sensitivity analysis is also a problem. Even when using an OAT approach, which is in principle nonlocal, moving one step at a time exploring one dimension at a time leaves a large portion of the input factors space unexplored, which for, e.g., a 10-dimensional problem can be shown[16a] to be >99% of the entire factors space.

Equation 7 can help, by allowing a combination of local derivatives and input factors variation. Yet to trust eq 7 on its own, without a check of the linearity of the system, would be unwarranted. A quick glance at the space of the input, even with a handful of data points as done by our regression analysis with 64 points, is straightforward and safer. The model coefficient of determination can help to identify problems, such as, e.g., a nonmonotonicity between input and output (Figure 6), which would result in low or zero β_i and S^{σ}_i even for an influent factor X_i. In this case, in order to build a regression-based sensitivity analysis, one would have to look at various trial nonlinear regression models,[61,70,70a] e.g., via a brute force search for the most convenient regression variables (and combinations of). Software packages are available to do that, but the search may be computationally expensive. Finally one might combine Monte Carlo and derivative by computing derivatives at different points.[18a,b] As we shall see later, this method can complement the variance-based approach described next.

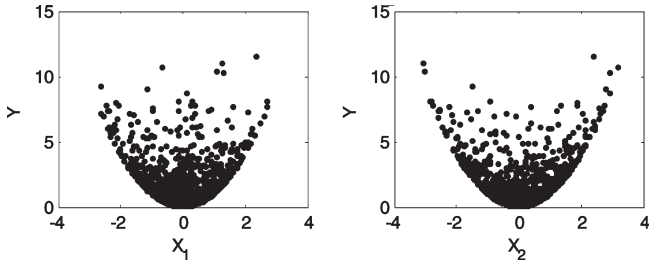


Figure 6. Scatter plot for model $Y = \Sigma_{i=1}^{k} \alpha_i X_i^2$ and $X_i \approx N(0,1)$ for all i's. β_i's are zero for this model ($k = 2$; $\alpha_i = 1$ in the plots). FAST indices are instead $S_i = \alpha_i^2/\Sigma\alpha_i^2$.

2.3. Variance-Based Methods ~~Fourier Amplitude Sensitivity Test (FAST)~~

Variance-based sensitivity analysis methods work irrespective of the degree of linearity or additivity of the model. Let us call S_i the variance-based sensitivity index for a generic factor X_i which feeds into a model $Y = f(X_1,X_2,...,X_k)$ with k independent uncertain factors. It is standard practice[2] to ~~We can~~ assume that all factors are continuous random variables uniformly distributed in $[0,1]$(~~This is standard practice.[2] Input factors can then be mapped from the unit hypercube to their actual distribution.~~), so that the space of definition of f is a unit hypercube in k dimensions. Input factors can then be mapped from the unit hypercube to their actual distribution. This mapping can also be built for discrete or even qualitative inputs, although FAST-based methods are not suggested in this case.[53]

We plan to illustrate that S_i is a model-free extension of the standard regression coefficients β_i, in the sense that $S_i = \beta_i^2$ for linear models.

Before showing how S_i can be computed numerically using ~~Fourier analysis~~ FAST or Monte Carlo, a possibly intuitive description is now given. We ask ourselves if we can reduce the uncertainty in Y by removing the uncertainty (e.g., by measurement) in some of the X_i's. There will surely be factors more promising than others for this kind of analysis. Let us call $V(Y)$ the variance of Y, and $V_{\mathbf{X}_{-i}}(Y|X_i = X_i^*)$ the variance that we would obtain if we could fix X_i to some value. The subscript $\mathbf{X}_{-i}$ of V is to remind us that this variance is taken over all factors other than X_i, which is fixed.

X_i^* could be the true value of X_i determined with a measurement. ~~If we could compute $V_{\mathbf{X}_{-i}}(Y|X_i = X_i^*)$ for all factors at all points, we would surely find the one with the smallest~~

~~$V_{\mathbf{X}_{-i}}(Y|X_i = X_i^*)$, but at this point, we would be past sensitivity analysis, having determined all uncertain factors.~~ What can we do before having actually taken the measure, i.e., before knowing X_i^*? A natural answer is the average of $V_{\mathbf{X}_{-i}}(Y|X_i = X_i^*)$ over the possible values of X_i^*. We would write this as $E_{X_i}(V_{\mathbf{X}_{-i}}(Y|X_i))$. We have dropped the dependency from X_i^*, as the quantity $E_{X_i}(V_{\mathbf{X}_{-i}}(Y|X_i))$ is independent of any particular point in the distribution of X_i. ~~This quantity is relevant to the solution of the problem just posed; i.e.~~ Thus, the factor with the smallest $E_{X_i}(V_{\mathbf{X}_{-i}}(Y|X_i))$ is now the desired most promising candidate for measurement, in terms of expected reduction of the variance of Y. A known algebraic result is that

$$V(Y) = E_{X_i}(V_{\mathbf{X}_{-i}}(Y|X_i)) + V_{X_i}(E_{\mathbf{X}_{-i}}(Y|X_i)) \quad (12)$$

so that the smallest $E_{X_i}(V_{\mathbf{X}_{-i}}(Y|X_i))$ will correspond to the largest $V_{X_i}(E_{\mathbf{X}_{-i}}(Y|X_i))$. The ~~FAST~~ variance-based sensitivity index is simply

$$S_i = \frac{V_{X_i}(E_{\mathbf{X}_{-i}}(Y|X_i))}{V(Y)} \quad (13)$$

Equation 13 has been discussed by Pearson as early as 1905 under the name of correlation ratio.[65b]

S_i is hence the educated answer to the question: "If one wants to reduce the variance of the output, which factors should be fixed first?" We have called this question "factor prioritization setting" ~~and have argued that such a framing of the sensitivity analysis with respect to a setting allows an otherwise vague concept of factor importance to be clarified.~~[45,54] In sensitivity analysis a setting allows the analyst to specify what is meant by "factor's importance" for a particular application.[45,54] Leaving instead the concept of importance undefined could result in several tests being thrown at the problem and in several rankings of factor importance being obtained, without a basis to decide which one to believe.

As stressed in ref 54, the "factor prioritization" setting has to be considered in a betting context. Therefore, there is no warranty that fixing the most important factor at a given value within its range will reduce the response variance. In some instances, for nonadditive models, the response variance could even be augmented.

The values of S_{k_1} and $S_{k_{-1}}$ for the model in eq 2 would practically coincide with the β_i of Figure 5, due to model's quasi-linearity (shown by the very high R^2 for every t), and hence, we do not plot them here. Before introducing the next model, which will make these measures worth using, we briefly illustrate two computational strategies to estimate eq 13: FAST and the method of Sobol'.

2.4. FAST-Based Methods

When using FAST,[20−27] S_i is computed by exploring the k-dimensional space of the input factors with a search curve defined by a set of parametric equations

$$x_i = G_i(\sin(\omega_i s)) \quad (14)$$

with $i = 1, 2, ..., k$, where s is a scalar varying in $(-\infty,+\infty)$, the ω_i are a set of different angular frequencies associated with each factor, and the G_i are properly selected transformation functions (e.g., $x_i = 1/2 + \arcsin(\sin(\omega_i s))/\pi$ is used in ref 53). Scanning eq 14 for different values of s results in a curve in the k-dimensional hypercube whereby each dimension is explored with a different frequency ω_i. Fourier analysis of the signal derived from the values of the output Y along this curve allows the computation of $V_{X_i}(E_{\mathbf{X}_{-i}}(Y|X_i))$, on the basis of the signal at ω_i and few of its higher harmonics. The implementation of the method requires care, mostly in avoiding interferences, based on accurate selection of the set of k frequencies ω_i.[26,27] Extensions of the FAST method are described in refs 53 and 66.

Cukier and co-workers[23] noted that the FAST indices could be seen as the first-order terms in the decomposition of the unconditional variance, which for independent factors can be written as

$$V(Y) = \sum_i V_i + \sum_{i<j} V_{ij} + \sum_{i<j<l} V_{ijl} + ... + V_{123...k} \quad (15)$$

where

$$V_i = V_{X_i}(E_{\mathbf{X}_{-i}}(Y|X_i)) \quad (16)$$

$$V_{ij} = V_{X_iX_j}(E_{\mathbf{X}_{-ij}}(Y|X_i, X_j)) - V_i - V_j \quad (17)$$

$$V_{ijl} = V_{X_iX_jX_l}[E_{\mathbf{X}_{-ijl}}(Y|X_i, X_j, X_l)] - V_{ij} - V_{jl} - V_{il} - V_i - V_j - V_l \quad (18)$$

Note that in writing, e.g., $V_{X_iX_j}(E_{\mathbf{X}_{-ij}}(Y|X_i,X_j))$ we mean that the inner expectation is over all factors but X_i,X_j and the outer variance is over X_i,X_j.

In classic FAST (e.g., refs 25 and 26) only the main effect terms S_i are computed, and the success of a given analysis is empirically evaluated by the sum of these terms: if this is high, as a rule of the thumb greater than 0.6,[30] then the analysis is successful (i.e., we have explained more than 60% of the variance of the output).

The V_i describe the so-called "additive" part of a model. In turn, additive models are defined as those for which $\Sigma_i S_i = 1$. Extended FAST[53] allows the computation of higher order terms.

It is easy to verify[45] that for linear models both relations $\Sigma_i\beta_i^2 = 1$ and $\Sigma_i S_i = 1$ hold. Yet the second relationship holds also for models that are nonlinear albeit additive. To make a trivial example, $Y = \sum_{i=1}^{k} \alpha_i X_i^2$ is nonlinear and nonmonotonic if the distribution function of the X_i's is centered at zero (Figure 6). Yet, this is an additive model, for which $V(Y) = \Sigma_i V_i$ and $\Sigma_i S_i = 1$. For our almost linear model (eq 2), $\Sigma_i S_i = S_{k_1} + S_{k_{-1}} = 0.995$ at $t = 0.06$ and $= 0.991$ at $t = 0.3$, while the remaining bit of variance, $S_{k_1k_{-1}} = 0.005-0.009$ for t in $[0,0.3]$, describes the insignificant interaction effect of k_1 and k_{-1}. In experimental design, $S_{k_1k_{-1}}$ is also known as a second-order or two-way effect.

Unlike the case of local sensitivity analysis, where the cost of computing a second-order term is, in general, affordable,[3] terms of higher order in eq 15 are seldom used in global sensitivity analysis, because of their number and computational cost. There are in fact $\binom{k}{2}$ terms of the second-order (V_{ij}), $\binom{k}{3}$ terms of the V_{ijl} type, and so on, for a total of $2^k - 1$ terms in eq 15. This problem is known among practitioners as "the curse of dimensionality". It has been argued[46,47] that terms above the second-order ones should not be too frequent in sound models of physical systems, but we find this assumption unsafe.

The computation of the first-order sensitivity indices using FAST today can be greatly accelerated using random balance designs[36a,66] (RBDs), which is the method we recommend as a good practice.

dx.doi.org/10.1021/cr200301u |Chem. Rev. 2012, 112, PR1–PR21

The estimator of RBDs is exactly the same as in FAST; however, the sampling strategy is different. Let us illustrate this procedure on a simple example with $N = 8$ points and $k = 2$ model inputs. We first select N equally distributed points within the range $(-\pi, \pi)$:

$$\mathbf{s} = \left| -\frac{7}{8}\pi \; -\frac{5}{8}\pi \; -\frac{3}{8}\pi \; -\frac{1}{8}\pi \; \frac{1}{8}\pi \; \frac{3}{8}\pi \; \frac{5}{8}\pi \; \frac{7}{8}\pi \right| \tag{19}$$

Two independent random permutations of its elements are obtained:

$$\begin{aligned} \mathbf{s}_{1,j} &= \left| -\frac{1}{8}\pi \; -\frac{3}{8}\pi \; \frac{5}{8}\pi \; -\frac{7}{8}\pi \; \frac{7}{8}\pi \; \frac{1}{8}\pi \; -\frac{5}{8}\pi \; \frac{3}{8}\pi \right| \\ \mathbf{s}_{2,j} &= \left| \frac{7}{8}\pi \; -\frac{3}{8}\pi \; \frac{1}{8}\pi \; -\frac{7}{8}\pi \; \frac{5}{8}\pi \; -\frac{5}{8}\pi \; \frac{3}{8}\pi \; -\frac{1}{8}\pi \right| \end{aligned} \tag{20}$$

Finally, the design points (uniformly distributed within 0 and 1) are obtained by applying the transformation

$$x_{i,j} = \frac{1}{2} + \frac{1}{\pi}\arcsin(\sin s_{i,j}), \quad \forall i = 1,2 \; \forall j = 1,2,\ldots,8 \tag{21}$$

to the vectors s_1 and s_2, obtaining the following sample matrix x with 2 rows and 8 columns:

$$\mathbf{x} = \left| \begin{matrix} \mathbf{x}_1 \\ \mathbf{x}_2 \end{matrix} \right| = \left| \begin{matrix} \frac{3}{8} & \frac{1}{8} & \frac{7}{8} & \frac{3}{8} & \frac{5}{8} & \frac{5}{8} & \frac{1}{8} & \frac{7}{8} \\ \frac{5}{8} & \frac{1}{8} & \frac{5}{8} & \frac{3}{8} & \frac{7}{8} & \frac{1}{8} & \frac{7}{8} & \frac{3}{8} \end{matrix} \right| \tag{22}$$

Consider that the symmetry of the sine function with respect to $x = \pm \pi/2$ can produce same $x_{i,j}$ values for different $s_{i,j}$ points: for example, $s_{i,j} = (3/8)\pi$ and $s_{i,j} = (5/8)\pi$ correspond to $x_{i,j} = (7/8)$. Now, the model f is evaluated at each column of the sample matrix $\mathbf{x}$

$$y_j = f(x_{1,j}, x_{2,j}) \quad \forall j = 1,2,\ldots,8 \tag{23}$$

obtaining a row vector

$$y = \left| y_1 \; y_2 \; y_3 \; y_4 \; y_5 \; y_6 \; y_7 \; y_8 \right|. \tag{24}$$

The first-order sensitivity measure for X_1 is obtained by calculating the Fourier spectrum of this series:

$$y^{R_1} = \left| y_4 \; y_3 \; y_7 \; y_1 \; y_8 \; y_5 \; y_2 \; y_6 \right| \tag{25}$$

which is a resorting of the output values $\{y_i\}$ $\forall j = 1, 2, \ldots, N$ such that the elements of the corresponding vector $\mathbf{s}_1$ appear in increasing order (exactly as the vector $\mathbf{s}$). Then, for X_2, the $\{y_i\}$ have to be resorted as

$$y^{R_2} = \left| y_8 \; y_3 \; y_5 \; y_1 \; y_7 \; y_2 \; y_6 \; y_4 \right| \tag{26}$$

such that the elements of s_2 are in increasing order. In general, for k inputs, there are k independent random permutations of $\mathbf{s}$, and k resortings of $\{y_i\}$.

In summary, the first-order sensitivity measure for input X_i is estimated by

(i) reordering the model outputs such that the design points are in increasing order with respect to input X_i;
(ii) calculating the Fourier spectrum of the reordered model output at frequencies 1, 2, ..., M (generally, $M = 6$);
(iii) summing up the amplitudes of the Fourier spectrum;
(iv) dividing by the total unconditional variance of the model output.

This four-step procedure is repeated for each input X_i to obtain all the other sensitivity measures. If one is only interested in the estimation of the first order indices, we suggest using RBD, more efficient than the method of Sobol' (see next section), as each model run contributes to the estimation of all the sensitivity indices.

RBD has a number of other advantages with respect to FAST: no problem of aliasing, hence the absence of a lower limit for the size of N; no need to have an algorithm for the calculation of frequencies free of interferences; and estimates are more accurate than FAST as potential interference effects are absent. One final caveat about FAST is that it is impractical if the input factors are sampled from discrete distributions.[53]

2.5. Monte Carlo Implementation of Variance-Based Methods ~~Monte Carlo-Based Version of FAST and the Work of Sobol'~~

Several Monte Carlo-based estimates of the first-order terms V_i have been proposed.[37−44] It will be sufficient here to consider the work of Sobol'.[42] Sobol' moves from a decomposition of the function/model terms of increasing dimensionality, i.e.,

$$\begin{aligned} Y &= f(X_1, X_2, \ldots X_k) \\ &= f_0 + \sum_i f_i(X_i) + \ldots + \sum_{i<j} f_{ij}(X_i, X_j) + \ldots f_{12\ldots k} \end{aligned} \tag{27}$$

There are infinite ways of decomposing f, but for independent factors there is a unique decomposition in orthogonal terms which ensures:

$$\begin{aligned} V_i &= V_{X_i}(f_i) \\ V_{ij} &= V_{X_iX_j}(f_{ij}) \end{aligned} \tag{28}$$

and so on. The f_i's, f_{ij}'s, ... are known as terms of the ANOVA-HDMR,[46] where HDMR stands for high-dimensional model representation and ANOVA refers to the analysis of variance from experimental design.[48] In particular $f_i = E(Y|X_i) - E(Y)$, and $f_{ij} = E(Y|X_iX_j) - E(Y|X_i) - E(Y|X_j) + E(Y)$, where $E(Y) = f_0$ and so on for higher-order terms.[42] As discussed in section 2.10 (and Figure 3), f_i can be estimated from smoothing splines and used for sensitivity analysis.[75]

Sobol' offered a Monte Carlo strategy to compute indices of any order, that is based on a Monte Carlo exploration of the input space. To make an example, to estimate V_i, the best available strategy is[65c]

$$\begin{aligned} \hat{V}_i = \frac{1}{N}\sum_{j=1}^{N} & f(x_{j1}^b, x_{j2}^b, \ldots, x_{jk}^b,) \\ & \times f(x_{j1}^a, \ldots, x_{j(i-1)}^a, x_{ji}^b, x_{j(i+1)}^a, \ldots, x_{jk}^a) - f_0^2 \end{aligned} \tag{29}$$

dx.doi.org/10.1021/cr200301u |Chem. Rev. 2012, 112, PR1–PR21

where N is the sample size of a MC simulation, k is the number of independent factors, and the superscripts a and b stand to indicate that two independent input matrices have been used:

$$\mathbf{A} = \begin{pmatrix} x_{11}^a & \cdots & x_{1k}^a \\ \cdots & \cdots & \cdots \\ x_{N1}^a & \cdots & x_{Nk}^a \end{pmatrix}, \quad \mathbf{B} = \begin{pmatrix} x_{11}^b & \cdots & x_{1k}^b \\ \cdots & \cdots & \cdots \\ x_{N1}^b & \cdots & x_{Nk}^b \end{pmatrix} \tag{30}$$

and for each factor a new matrix is built taking all columns from matrix **A**, but for column i which is taken from matrix **B**.

$$\mathbf{A}_b^i = \begin{pmatrix} x_{11}^a & \cdots & x_{1(i-1)}^a & x_{1i}^b & x_{1(i+1)}^a & \cdots & x_{1k}^a \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ x_{N1}^a & \cdots & x_{N(i-1)}^a & x_{Ni}^b & x_{N(i+1)}^a & \cdots & x_{Nk}^a \end{pmatrix} \tag{31}$$

Equation 29 says that in order to compute $\hat{V}_i$ one has to resample all factors but X_i. While it takes some reasoning[67] to demonstrate that $\hat{V}_i$ is an estimate of the partial variance $V_{X_i}(E_{\mathbf{X}_{-i}}(Y|X_i))$, it is intuitive that $\hat{V}_i$ is large when X_i is influent. If X_i controls the output, then large values of f will be multiplied with one another in eq 29, and the same is true for low values. If X_i is noninfluent, low and high values of f will be randomly combined, resulting in a lower value of $\hat{V}_i$. We suggest a sequential approach for the evaluation of the above indices, whereby new model evaluations are executed only if the user needs to increase the precision of the estimates: the rows of matrices of eq 30 are augmented until the desired convergence is achieved.

Sobol' noted that an important objective of the sensitivity analysis is to identify those factors that have no ~~sensible~~ important effect on the output. To tackle the problem, he rewrote eq 15 for sets of factors as

$$V(Y) = V_{\mathbf{U}}(E_{\mathbf{Z}}(Y|\mathbf{U})) + V_{\mathbf{Z}}(E_{\mathbf{U}}(Y|\mathbf{Z})) + V_{\mathbf{UZ}} \tag{32}$$

where all factors in **X** have been partitioned in two sets, (1) a trial set **U** of supposedly noninfluential factors and (2) the remaining factors **Z**. $V_{\mathbf{UZ}}$ is the pure interaction effect between the two sets and can be easily computed by difference. If $V(Y) = V_{\mathbf{Z}}(E_{\mathbf{U}}(Y|\mathbf{Z}))$, then one can conclude that the set **U** is truly noninfluential. Note that the condition of noninfluence implies $V_{\mathbf{U}}(E_{\mathbf{Z}}(Y|\mathbf{U})) + V_{\mathbf{UZ}} = 0$, and not simply $V_{\mathbf{U}}(E_{\mathbf{Z}}(Y|\mathbf{U})) = 0$. We shall go back to this in section 2.7 ~~in a moment~~.

As mentioned in the Introduction, decompositions such as in eqs 15 and 27 are common in experimental design, where one varies control variables; e.g., for a chemical experiment one would vary temperature, catalyst, and concentrations among a set of pre-established levels (often just two, high and low, for each variable) as to maximize the number of effects (first order, second order, ...) one can determine for a given cost in terms of number of experiments.[48] More precisely, if we had sampled the points in the k-dimensional hypercube with a n^k factorial design as $\{0, 1/(n-1), ..., (n-2)/(n-1), 1\}$, thus forming a uniform grid, then the $f_i(X_i)$ of eq 27 would be identical to the ANOVA estimate of the main effect in a full factorial design.[33,48] It has also been suggested to use the functions in eq 27 directly for the purpose of sensitivity analysis.[49]

We have plotted in Figure 3 f_{k_1} and $f_{k_{-1}}$ for the model in eq 2. No other functions are needed for this model, as $[A] = f_{k_1} + f_{k_{-1}} + f_{k_1k_{-1}}$ is in this case $[A] \approx f_{k_1} + f_{k_{-1}}$ (as the reader can ascertain comparing the values of [A] in Figure 1 with f_{k_1} and $f_{k_{-1}}$ from Figure 3) and the interaction term $f_{k_1k_{-1}}$ is negligible.

This direct use of functional decompositions such as f_{k_i} for sensitivity analysis is elegant and informative, but employing the above-mentioned n^k factorial design can become impractical when the number of factors and/or of their nonzero interactions increases.

Representations such as eq 27 of multivariate functions by superposition of simpler functions such as projection pursuit, radial basis functions, and others are common in Mathematics[46] and have a long history.[47,68] This idea feeds in the strong recent development of meta-modeling-based sensitivity analysis (see section 2.10). ~~Rabitz and co-workersfurther proposed an alternative model representation that is based on knowing the model values on lines, planes, and hyperplanes that pass through a selected point in the space of the input factors. He calls these cut-HDMR, to distinguish them from the ANOVA-HDMR of eq 11.~~

~~An example of cut-HDMR for the model in eq 1 is also in Figure 3, together with the Taylor expansion (based on local derivatives at the midpoint) of the same factors.~~

~~The three model representations are substantially equivalent for this quasi-linear model.~~

~~The cut-HDMR has been applied to chemical problems. An interesting property of the cut-HDMR is that it can be used as a basis for efficiently computing the ANOVA-HDMR (the terms in eq 11). We shall discuss the merits of the HDMR with an application in the next section. Yet, the method still depends on the assumption that in eq 13 terms of order higher than two or three are negligible.~~

2.6. The Second Test Case

We move now to show that it is better to have global sensitivity analysis in terms of FAST or Monte Carlo estimates of S_i, rather than in terms of β_i or derivatives. [Although, as discussed in section 2.2, S_i^{σ} and β_i can provide an approximate estimate of S_i.] To do this, we introduce our second example.

This is a thermal runaway analysis of a batch reactor, with exothermic reaction A → B

$$\frac{\mathrm{d}[A]}{\mathrm{d}t} = -k(T)[A]^n \tag{33}$$

where n is the order of the reaction, and

$$\rho c_v \frac{\mathrm{d}T}{\mathrm{d}t} = (-\Delta H)k(T)C^n - s_v u(T - T_a) \tag{34}$$

where ρ is the density of the fluid mixture [kg/m^3], c_v is the mean specific heat capacity of the reaction mixture [J/(K mol)], ΔH is the molar reaction enthalpy [J/mol], s_v is the surface area per unit volume [m^2/m^3], u is the overall heat transfer coefficient [J/(m^2 s K)], and T_a is the ambient temperature.

The initial conditions are $[A] = [A]_0$, $T = T_0$, and $t = 0$.

The model can be ~~is customarily~~ rewritten in dimensionless form:

$$\frac{\mathrm{d}x}{\mathrm{d}\tau} = \exp\left(\frac{\theta}{1 + \theta/\gamma}\right)(1-x)^n = F_1(x,\theta)$$
$$\frac{\mathrm{d}\theta}{\mathrm{d}\tau} = B\exp\left(\frac{\theta}{1 + \theta/\gamma}\right)(1-x)^n - \frac{B}{\psi}(\theta - \theta_a) = F_2(x,\theta) \tag{35}$$

dx.doi.org/10.1021/cr200301u |Chem. Rev. 2012, 112, PR1–PR21

with initial conditions (IC's) $x = 0$ and $\theta = 0$, at $\tau = 0$, and the dimensionless variables

$$x = \frac{[A]_0 - [A]}{[A]_0}; \quad \theta = \frac{T_0 - T}{T_0}\gamma; \quad \tau = tk(T_0)([A]_0)^{n-1} \tag{36}$$

and dimensionless parameters:

$$B = \frac{(-\Delta H)[A]_0}{\rho c_v T_0}\gamma: \quad \text{dimensionless heat of reaction}$$

$$\gamma = \frac{E}{R_g T_0}: \quad \text{dimensionless activation energy}$$

$$\psi = \frac{(-\Delta H)k(T_0)([A]_0)^n}{s_v u T_0}\gamma: \quad \text{Semenov number}$$

$$= (\text{heat release potential})/(\text{heat removal potential})$$

This system has been widely analyzed in the last century to characterize thermal runaway at varying operating conditions.[8] At given rate constant and ambient temperature, the system is completely determined by the parameters B and ψ, and critical conditions are usually illustrated in the $B-\psi$ parameter plane.

A reactor under explosive conditions is sensitive to small variations in, e.g., the initial temperature, while, under nonexplosive conditions, the system remains insensitive to such variations. Thus, boundaries between runaway (explosive) and nonrunaway (nonexplosive) conditions can be identified on the basis of its sensitivity to small changes in the operating parameters. The system can also be characterized by the derivative of the maximum temperature reached in the reactor versus the initial temperature, i.e.,[73] $S(\theta^*,\theta_0) = d\theta^*/d\theta_0$.

The runaway boundary is defined as the critical value of each parameter for which the sensitivity to the initial condition is maximum; e.g., for the Semenov number ψ, we have the results in Figure 7.

For ψ values smaller than ψ_c, the system is in nonrunaway conditions; i.e., the maximum temperature reached in the reactor is not very high, and this maximum is insensitive to small variations in the inlet temperature. With an increase in ψ, both the maximum temperature and its sensitivity to T_0 smoothly increase until, in proximity to ψ_c, there is a sharp rise for both of them that rapidly brings the reactor to a strong temperature increase. For ψ values higher than ψ_c, the sensitivity goes back to smaller values, leaving unchanged the extreme temperature rise reached at ψ_c. From this, fixing reaction kinetic (n,γ) and ambient temperature (θ_a), the curve in the $B-\psi$ plane can be obtained (Figure 8).

Let us consider the case of a system with nominal parameter design $B = 20$, $\gamma = 20$, $n = 1$, $\theta_a = 0$, and $\psi = 0.5$. Under these conditions, the system should be within the nonrunaway region. The system, however, is characterized by uncertainties. So, let us assume the following probability density functions for model parameters:

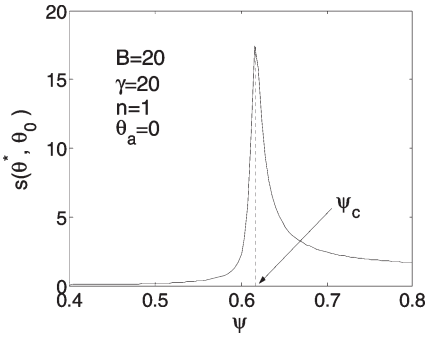


Figure 7. $S(\theta^*,\theta_0) = d\theta^*/d\theta_0$ versus Semenov number ψ for model (33, 37).

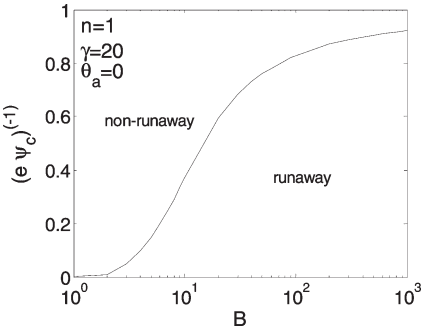


Figure 8. Runaway versus nonrunaway in the plane $B,1/e\psi$ for fixed (n,γ) and (θ_a) (e is the number of Neper).

$$\begin{aligned} B &\sim N(20,4) \\ \gamma &\sim N(20,2) \\ \psi &\sim U(0.4,0.6) \\ \theta_a &\sim N(0,0.2) \\ \theta_0 &\sim N(0,0.2) \end{aligned} \tag{37}$$

where U indicates a uniform distribution and N is a normal distribution with mean and standard deviation represented by the first and second coefficients in parentheses.

Under the chosen operating conditions ($\gamma = 20$), a 0.02 standard deviation for the ambient and initial dimensionless temperatures corresponds to an about 30 K standard deviation in the absolute temperature scale.

We perform a Monte Carlo simulation, whose total cost is 6 144 model evaluations (see section 2.7 for computational details; here, again, we choose an arbitrary number of sample points. A rule of thumb for the selection of an initial sample size is available.[11a]), and analyze the behavior of the temperature maximum. In Figure 9 we can see that, even if the nominal conditions of the reactor are stable, there are threshold values for B, θ_a, and ψ for which the maximum temperature in the reactor can have a sharp rise (absolute temperature can double, with a rise of, e.g., 300 K). This striking result vindicates the use of global (e.g., Monte Carlo) exploration methods for uncertainty analysis even in the presence of moderate factors uncertainty. This result is due to the nonlinear and nonadditive nature of

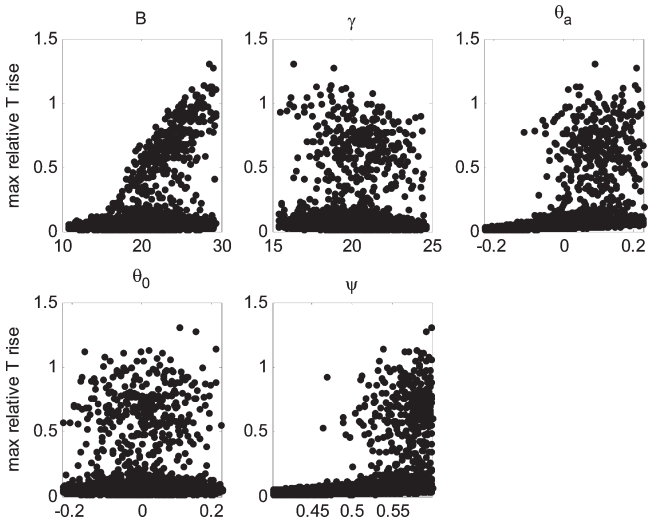


Figure 9. Relative temperature change at the maximum $[(T^{max} - T_0)/T_0]$ versus the uncertain model parameters. A rise in the ordinate to about 1.2 corresponds to a temperature shift of about 300 K for the operating conditions assumed.

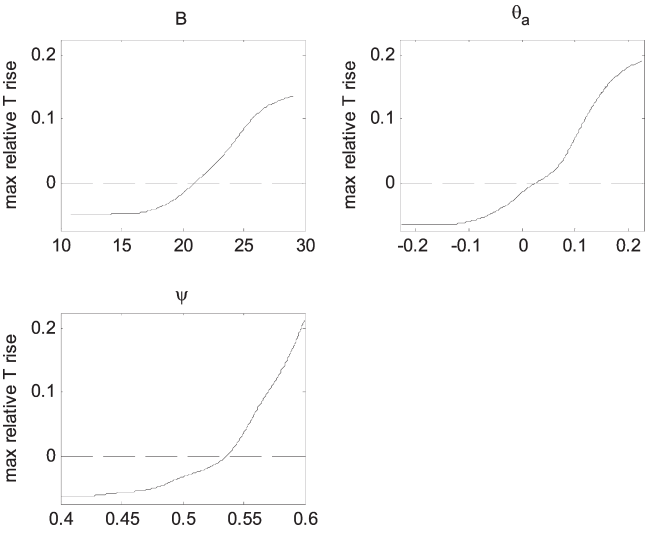


Figure 10. Most significant first-order ANOVA-HDMR terms f_B, f_{θ_a}, and f_ψ when the output is the maximum relative temperature rise $(T^{max} - T_0)/T_0$ (mean value of $(T^{max} - T_0)/T_0$ is 0.1) estimated through smoothing splines.[75] All the lines have zero mean; i.e., ANOVA-HDMR functions plot the change with respect to the overall mean (which is about 0.1). The sample size used for smoothing splines estimation was 512.

Table 1. Sensitivity Measures for Model (eqs 33−37) (Total Number of Simulations Used to Compute S_i and S_{Ti} is 6 144; 512 Simulations Were Used for β_i^2)

	β_i^2	S_i	S_{Ti} (introduced in section 2.7)
Ψ	0.176	0.178	0.674
θ_a	0.117	0.164	0.556
B	0.104	0.080	0.469
γ	0.003	0.002	0.032
θ_0	0.002	0.002	0.013
sum	0.402	0.426	

the problem, as shown by the different sensitivity measures for θ^* (see Table 1).

Let us look at the β_i^2 and S_i in Table 1 first. The sensitivity based on the β_i's can only capture 40% of the variation of the maximum temperature. Considering the variance-based main effects, we can arrive at 43%. This implies a 57% interaction between the model parameters. We could stop the analysis at this point, or we might pursue our investigation to achieve a full mapping of the input/output relationship. Stopping here would mean that we are happy with having learned that the parameter which offers a better chance of reducing the variance in the maximum temperature is ψ. Yet, this factor only accounts for ~18% of the variance, and the large unknown interactions might suggest that a much larger reduction in variance can be achieved if one could identify the interacting factors and try to fix them.

One avenue to do that would be to compute individual interaction terms.[74,75] In this example all the second- and third-order interaction terms could be computed at no extra cost; see also section 3.[74] The full variance decomposition in this example could be obtained with a total cost of 6 144 model runs. If only first-order indices were of interest, only a single shot of 500 runs would be sufficient, applying ~~the method of Ratto et al.~~ either RBD or any of the meta-modeling methods discussed in section 2.10. To compute only first and total effects (see section 2.7 next), leaving out second-order effects from the analysis, 3 000 runs would have been sufficient. For this example, meta-modeling is also able to provide quite accurately the full decomposition and the total effects (see section 2.10).] We get that the most significant second-order interaction terms $S_{ij} = V_{ij}/V(Y)$ are $S_{B\psi} = 0.17$, $S_{\psi\theta_a} = 0.17$, and $S_{B\theta_a} = 0.166$. Given that B, θ_a, and ψ seem to be the factors that interact the most, we may further compute the overall effect of these three factors. This comes out to be 0.961, i.e., almost the total variance. [Note that the sum of all effects of the factors B, θ_a, and ψ is made of their first-order terms, plus the three second-order terms, plus the single third-order term. This sum can also be written as $V_{\psi,B,\theta_a}(E_{\gamma\theta_0}(Y|\psi,B,\theta_a))/V(Y)$ and computed as such, i.e., without computing all the terms.]~~, i.e., almost the total variance.~~ If we measure the third-order interaction term, we obtain $S_{\psi,B,\theta_a} = 0.032$.

This example points to the importance of identifying interactions in sensitivity analysis.

~~We now apply to the example both ANOVA- and cut-HDMR.~~ In Figure 10 we show the approximated first-order ANOVA-HDMR terms f_B, f_{θ_a}, and f_ψ for the most important factors, obtained using smoothing splines.[75] These show that the first-order relationships are monotonic, which explains why β_i^2 gives an acceptable estimate of the first-order sensitivities in Table 1, with an overall error of about 0.03.

~~In Figure 10 we also show the approximated ANOVA-HDMR terms f_i, obtained by passing through the third-order cut-HDMR expansion of the most important factors (B,θ_a,ψ). The approximation is fairly good and illustrates the standard usage of cut-HDMR, i.e., as an efficient way to estimate the ANOVA-HDMR, such as f_i.~~

In Figure 11 we show the approximated second-order ANOVA-HDMR terms of the subset (B,θ_a,ψ), again obtained through ~~cut-HDMR~~ smoothing splines.[75] All statistics (β_i^2, S_i, and S_{Ti}) are obtained using a quasi-Monte Carlo sample of dimension 512: the approximation is fairly good and illustrates one advantage of meta-modeling, which not only provides estimates for

dx.doi.org/10.1021/cr200301u |Chem. Rev. 2012, 112, PR1–PR21

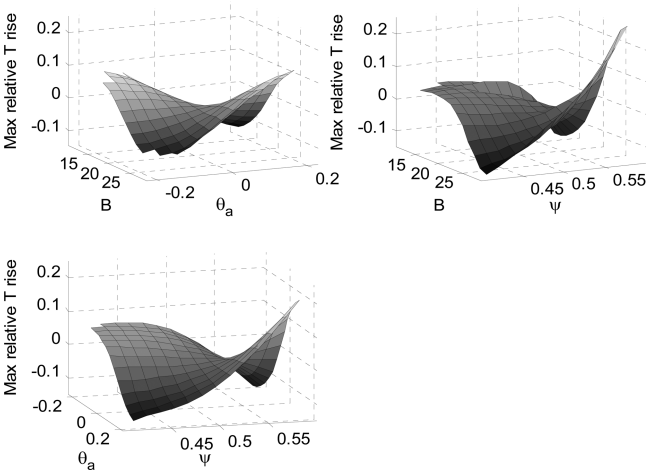


Figure 11. Most significant second-order ANOVA-HDMR terms of the maximum relative temperature rise, estimated through a smoothing splines ANOVA model.[75] The sample size used for estimating the metamodel was 512.

sensitivity indices but also is an efficient way to estimate the ANOVA-HDMR.

~~The grid of points for the cut-HDMR expansion up to the third order was of size 16 for each factor, for a total cost of 4912 runs.~~

2.7. Total Sensitivity Indices

Is there a more compact way to analyze the model in eqs 33−37 without computing all $(2^5 - 1) = 31$ terms of our 5-factor model? Surely for larger dimensionalities of the input factors space, a more compact measure would be useful. This is offered by another variance-based measure, which was implicit in our discussion of the Sobol' "group" sensitivity (eq 32), though it was introduced formally in ref 43. Imagine that the set $\mathbf{U}$ in eq 32 contains only one factor, X_i, and that as a result $\mathbf{Z} = \mathbf{X}_{-i}$. Hence, eq 32 becomes

$$V(Y) = V_{X_i}(E_{\mathbf{X}_{-i}}(Y|X_i)) + V_{\mathbf{X}_{-i}}(E_{X_i}(Y|\mathbf{X}_{-i})) + V_{X_i\mathbf{X}_{-i}} \tag{38}$$

The condition for X_i to be truly noninfluential is that $V_{X_i}(E_{\mathbf{X}_{-i}}(Y|X_i)) + V_{X_i\mathbf{X}_{-i}} = 0$, which is the same as $V(Y) - V_{\mathbf{X}_{-i}}(E_{X_i}(Y|\mathbf{X}_{-i})) = 0$. Because of eq 12, this is the same as to say that $E_{\mathbf{X}_{-i}}(V_{X_i}(Y|\mathbf{X}_{-i})) = 0$. In summary, if X_i is noninfluential, then $S_{Ti} = E_{\mathbf{X}_{-i}}(V_{X_i}(Y|\mathbf{X}_{-i}))/V(Y) = 0$. We call S_{Ti} the total sensitivity index of factor X_i. It is easy to prove[45] that the condition S_{Ti} is necessary and sufficient for X_i to be noninfluential. The descriptive power of this measure is evident by looking at the last column of Table 1. Even if we had not computed all second- and third-order interaction effects, it would now be evident from the difference between the S_i and S_{Ti} values for each factor that B, θ_a, and ψ are involved in significant interactions. From the total indices we can also see that all the interaction terms of factor γ with (B,θ_a,ψ) cover most of the 3.9% of total variance unexplained by the group (B,θ_a,ψ). Other advantages of the S_{Ti} measure are as follows:

(i) With S_{Ti}, we no longer have to limit our analysis to additive models.

(ii) It dispels the curse of dimensionality. One does not need to calculate all the $(2^k - 1)$ terms in eq 15 but just the $2k$ measures S_i and S_{Ti}, to obtain a good characterization of the system.

(iii) S_{Ti} can be computed using extended FAST[53] or more easily using the extended Sobol' methods.[74,65c] Attempts are ongoing to estimate total indices with RBD.[65d]

(iv) When eq 15 holds, e.g., when the input factors are independent, S_{Ti} can be easily seen to be equal to the sum of all terms (first-order plus interactions) that include factor X_i. For a simple three-factor model, this would imply that $S_{T1} = S_1 + S_{12} + S_{13} + S_{123}$.~~Even when the factors are not independent, S_{Ti} is an effective measure to use, e.g., if one wants to reduce the variance of the output acting on a subgroup of factors. It is intuitive that when interactions are present, a reduction in the variance of the output can be achieved by determining simultaneously the true values of two or more interacting factors.~~

~~Note that when one wants to criticize the use of S_i as a sensitivity measure, one usually builds a test case where a factor has a zero first-order term and important nonzero higher order terms. These criticisms are, in our opinion, unfounded, as S_i is the right measure to use for factors prioritization, as we discussed above. If one factor has a zero first-order term, no variance reduction can be expected by determining the true value of just that factor. On the other hand, if the analyst intends to identify noninfluential factors in order to remove them from the variance propagation analysis, then a broader concept of importance must be invoked, which corresponds to the S_{Ti} measure.~~

$S_{Ti} = E_{\mathbf{X}_{-i}}(V_{X_i}(Y|\mathbf{X}_{-i}))/V(Y)$ is, in fact, the expected variance that would be left if all factors but X_i were determined and provides the educated answer to the question, "Which factor can be fixed anywhere in its range of variability without affecting the output?", the answer being all those factors whose S_{Ti} is zero. We call this the "factors fixing" setting.[45]

Computing S_i and S_{Ti} for each factor X_i, while still being far from a full factors mapping, gives a fairly instructive description of the system.

It is evident that for independent input factors S_{Ti} will always be larger or equal to S_i. For nonindependent factors this is not the case because fixing a factor modifies the distributions of its correlated factors, which in turn may either increase or decrease the variance; see also ref 45, p 27. For nonindependent factors we still recommend to use S_i for factors prioritization. For factors fixing it may happen that S_{Ti} is zero for a given factor while its S_i is nonzero. This happens if Y is not a function of X_i while the joint pdf depends upon it. In this case both S_{Ti} and S_i must be zero for a factor to be fixed.

We give here our best recipe to compute simultaneously a full set of S_i and S_{Ti} for each factor X_i, based on refs 65c and 74. Note that this recipe is a good practice only if one wants to compute both sets of indices. To compute the S_i alone, the accelerated procedures described in sections 2.4 and 2.10 (e.g., RBD or metamodeling) should be used.

(i) Compute the model outputs corresponding to the two input matrices $\mathbf{A}$ and $\mathbf{B}$ (eq 30).

(ii) Compute the model outputs corresponding to the k matrices $\mathbf{A}_b^i$ which can be generated by replacing each column of $\mathbf{A}$ in turn with the corresponding column of $\mathbf{B}$. Steps (i) and (ii) cost $N(K + 2)$ runs in terms of model evaluations.

(iii) Compute S_i from the estimator given in eq 29 and S_{Ti} using the following estimator for $\widetilde{V}_{Ti}$:

$$\widetilde{V}_{Ti} = \frac{1}{2N}\sum_{j=1}^{N}\left(f\left(x_{j1}^{a}, x_{j2}^{a}, \ldots, x_{jk}^{a},\right) - f\left(x_{j1}^{a}, \ldots, x_{j(i-1)}^{a}, x_{ji}^{b}, x_{j(i+1)}^{a}, \ldots, x_{jk}^{a}\right)\right)^2 \quad (39)$$

With this recipe, in addition to the first-order and total indices computed with $(k+2)N$ model runs, all the interaction terms of order $(k-2)$ can be obtained at no extra cost.[74] At the additional cost of kN model runs, *double* estimates of all the first-order, second-order, $(k-2)$th order, and total indices can be obtained.[74] [This sampling design scheme has been applied in the test case of section 2.6, with $N = 512$ (this sample size was selected arbitrarily), $k = 5$, and an overall cost $(2k+2)$ N = 6144.] Finally, any other interaction term between the third and the $(k-3)$th can be estimated at the further additional cost of N model runs each.

When using Monte Carlo methods to estimate the sensitivity indices, random numbers can be used to generate the sample matrices **A** and **B** (eq 30) for the analysis. A valid alternative is to use quasi-random numbers (our recommended practice; scripts to generate them are available at ref 89]. These are sequences of multidimensional points characterized by "optimal" space-filling properties.[84,85]

A popular form of sampling that also aims to scan efficiently the input factors space is the Latin hypercube sampling (LHS), considered by some as the most effective strategy when the model is expensive to evaluate.[86] The space-filling properties of LHS can be enhanced by optimization algorithms, but their application can easily make calculations cumbersome.[49,49a]

The authors of the present review—based on several analyses using a battery of test functions—find quasi-random numbers superior to the LHS-based ones for the computation of sensitivity indices, although this depends both on the dimensionality of the problem and the property of the model (e.g., at high dimensionality all methods perform like purely random sampling; for a thorough discussion, see ref 86a). Because on the issue of the relative merits of LHS versus quasi-random sampling the community of practitioners is rather polarized, the reader is referred to the tools available at ref 89 for a direct analysis.Of course the estimators of eqs 29 and 39 work for purely random numbers as well.

As mentioned above, the couple of indices S_i and S_{Ti} can also be used when the input factors are not independent. Also in this case the indices are the right measure to use for the settings "prioritization" and "fixing",[54] although with nonindependent input factors the variance decomposition formula 15 no longer holds, the sum of the first indices is no longer bound to be <1, neither it is true in general that $S_i \leq S_{Ti}$[45] as discussed above.

Even for nonindependent factors, one can use the recipe above, with the added complication that all matrices **A**, **B**, and $\mathbf{A}_b^i$ must be drawn from appropriate conditional distributions, i.e., respecting the dependencies among factors.[65e]

An alternative unbiased estimation procedure for the nonindependent case is available for first-order indices and is based on *replicated* LHS.[87,88] This is also easy to code,[45] and the cost to estimate all the first-order indices is Nr model runs, where r is the number of replicates needed (usually at least 10) and the cost is independent of the number of factors. The convergence rate of this approach is slow: better precision of the sensitivity estimates can be attained only by increasing considerably both N and r.

Xu and Gertner overcome the independency limitation of the conventional FAST by extending the technique to models with correlated inputs.[88a] They proposed reordering the independent sample so that the sampled points honor the required correlation structure. Through the reordering, the variance contribution of both the input of interest and its correlation with other inputs is captured. Alternative indices for the sensitivity analysis with nonindependent inputs have been suggested in ref 47a. These indices are not linked to settings as the original S_i and S_{Ti}.[54]

As shown in section 2.10, meta-modeling-based estimation of total sensitivity indices is often achievable in practical cases, when the degree of interaction of the model at hand is not large. However, the procedure described in this section remains the only general recipe for total effects, which is applicable regardless of the complexity of the model.

2.8. A Screening Method ~~The Method of Morris~~

~~Another useful sensitivity measure, which is computationally less expensive than the variance-based methods, is the measure of Morris,[51] which is particularly suited when the number of uncertain factors is high and/or the model is expensive to compute. It belongs, thus, to the family of screening sensitivity analysis methods.[80]~~

At times the program code that computes the model's output is expensive to run, and/or there are many uncertain factors. In either case one may desire to obtain a first estimate of which factors do matter and which do not. This is a screening problem, for which the practice to compute the full set of indices S_i and S_{Ti} as described above can be impractical, as, e.g., one cannot afford the required number of model simulations.

In the literature the most popular method for screening is that of Morris.[51] Rather than describing this method in its original formulation[51] and variants,[82,82a] we offer here an alternative and more efficient approach[51a] that makes use of the same design described in section 2.7 for the S_{Ti} measure. Other screening designs, including supersaturated designs with fewer runs than factors, are described in ref 80.

To start, we reconsider the matrices in eq 30. The $N(k+2)$ points of matrices **A**, **B**, and $\mathbf{A}_b^i$, can be seen as "radial" design.[65c] Take the first row of **A** and the first rows of the k matrices $\mathbf{A}_b^i$. It is easy to say that these points can be viewed as a star, with the point from **A** at its core and the other k points as its rays. The same holds for rows from 2 to N, so that the **A** plus $\mathbf{A}_b^i$ design can be seen as made of N stars that span the input space. What about the additional N points from **B**? Each of these is a point made of pure "rays" coordinates. These points will not be needed for the screening design being introduced here. Note that this design (radial design or radial sampling in the following) can also be seen as an iterated OAT. In fact we will show that the radial design is a best-available practice in screening and that it is nothing other than an iteration of the OAT approach espoused by most modelers; in other words the best way to overcome the limitations of OAT is to iterate it at different points in the hyperspace of the input factors.[16a,51a]

When using the radial design for screening, we also suggest choosing carefully the points in the hyperspace, e.g., by using quasi-random numbers to locate the core of the stars.[51a] This implies using quasi-random numbers to generate matrix **A**. The design makes use of "elementary effects", where an elementary

dx.doi.org/10.1021/cr200301u |*Chem. Rev.* 2012, 112, PR1–PR21

effect is the absolute value of the incremental ratio computed over the ray of a star:

$$EE_i = \left| \frac{(f(A_b^i) - f(A))_i}{(A_b^i - A)_i} \right| \quad (40)$$

The radial screening measure is simply the average of the N elementary effects. The standard deviation of the same elementary effects can also be used as an additional indicator of the strength of nonlinear effects.

To illustrate this approach, we employ the dimethylsulfide (DMS) example mentioned in section 2.2. The model KIM[12,63] describes temperature-dependent tropospheric air and droplet chemistry for DMS. DMS chemistry is extensively investigated for its climatic implications.[81] In a work published in 1999, the KIM model included about 50 chemical reactions and 68 uncertain input factors, mostly kinetic and Henry law constants, which could be screened down to the 10 most important ones using the method of Morris.[82] The analysis was then completed by applying extended FAST to the 10 most important factors for a quantitative analysis using the S_i and S_{Ti} indices. ~~Here~~ In Figure 12, an updated version of KIM[83] is considered where the number of uncertain input factors is cut down to 56, and the sensitivity of the model is investigated via the ~~Morris method~~ radial design method.[51a] In an explanatory fashion, results are also compared with what would be obtained with a point derivative-based analysis.

~~The method of Morris varies one factor at a time across a certain number of levels selected in the space of the input factors. For each variation, a factor's elementary effect is computed, which is an incremental ratio for that factor:~~

~~A set of stepwise curves scan the factors levels, as to generate for each factor r different estimates of elementary effects u_i. The mean μ_i and the standard deviation σ_i of the elementary effects u_i over the r repetitions are used to assess the factors' importance. A high value of μ_i flags a high linear effect for a given factor, while a high value of σ_i flags either nonlinear or nonadditive factor behavior. It is useful also to compute the modulus version μ_i^* of the Morris method, i.e., the average of the $|u_i|$, and the importance of input factors is often assessed by plotting factors on the (μ_i^*, σ_i) axes (Figure 12). The factors closest to the origin are less influential.~~

~~μ_i^*~~ The screening test proposed here has similarities with the S_{Ti} index, in the sense that it tends to produce a ranking of the factors very similar or identical to that based on the S_{Ti} indices.[45] Looking at Figure 13 (comparative ranking for the input factors using $\partial Y/\partial X_i$, S_i^{σ}, and the average of the elementary effects) for the KIM model suggests that ranking of factors is markedly different when using derivative-based measures. If the rankings of the different measures were equal, we would have points in the left panel of Figure 13 aligned on a monotonic curve, while in the right panel points would stay on a straight line of unit slope. Conversely, both high and low importance factors are completely shifted if derivative-based measures are used. ~~Only the least important factors seem to have a similar ranking, even if significant changes are detected also in this case (see points in the gray oval in the right panel of Figure 13).~~

The lack of reliability of the derivative-based measures is due to the nonlinearity of the present version of the KIM model, as confirmed by performing a regression-based analysis through Monte Carlo simulation which generates a R^2 value of 0.57.

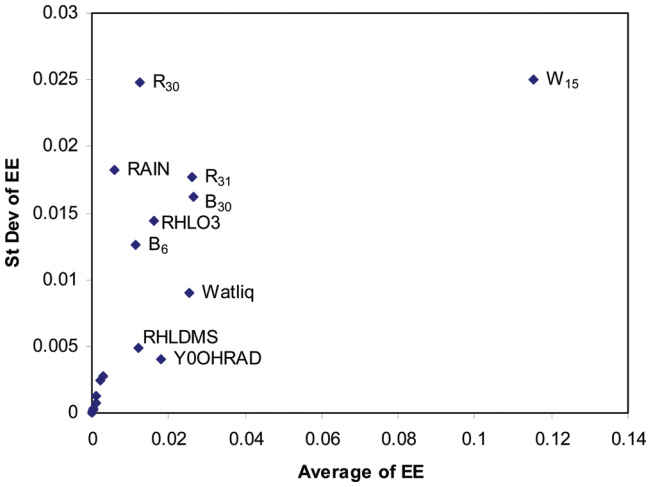


Figure 12. Screening of input factors based on the radial design. Factors away from the origin are the most important, while the factors clustered in (0,0) can be fixed. RHLO3 is the Henry's law constant for ozone (O_3). Watliq is the water liquid content. Y0OHRAD is the initial concentration of the OH radical. The R and B parameters represent rate constants of gas-phase reactions, while the W parameters indicate rate constants of liquid-phase reactions. A more detailed factors description is in ref 82.

The radial screening test presented here has a strong advantage with respect to other existing screening approaches: when the computational cost of the model allows it, the modeler can increase N, the number of repetitions, up to achieve a sample size compatible with the estimation of the global sensitivity index S_{Ti}. In this case one can replace the estimator average of the elementary effects with the estimator for S_{Ti} proposed in eq 39 to obtain a more accurate quantitative measure. Note that, for both radial screening and S_{Ti}, the cost of the analysis is $N(k + 1)$ [it becomes $N(k + 2)$ when both S_i and S_{Ti} need to be computed]. The difference is in the value of N, which can be as low as $N = 4$ for radial screening and on the order of hundreds/one thousand for S_{Ti}. The present approach thus offers a unified strategy for sensitivity analysis: the analyst can start with a small number of points (screening-wise) and then—depending on the results—possibly increase the numeral of points up to compute a fully quantitative measure.

Note that in the literature alternative methods are available for models with very high number of factors, such as supersaturated fractional factorial designs, where factors are iteratively perturbed in batches.[41,80] However, these methods preclude an effective exploration of the space of the inputs, as they mostly operate at very few factor levels and require strong assumptions on the model behavior. To make an example, Bettonvill, reviewed in ref 80, assumes that the input/output (I/O) function is known to be monotonic. ~~a known monotonic relationship between the output and each of the inputs.~~

2.9. Monte Carlo Filtering—~~An overview~~

~~Sensitivity analysis plays an important role in the verification of the formal correctness of models. It is rare to perform a SA without identifying model formal or coding errors, whose correction is thus made possible. For a discussion of the~~

dx.doi.org/10.1021/cr200301u |*Chem. Rev.* 2012, 112, PR1–PR21

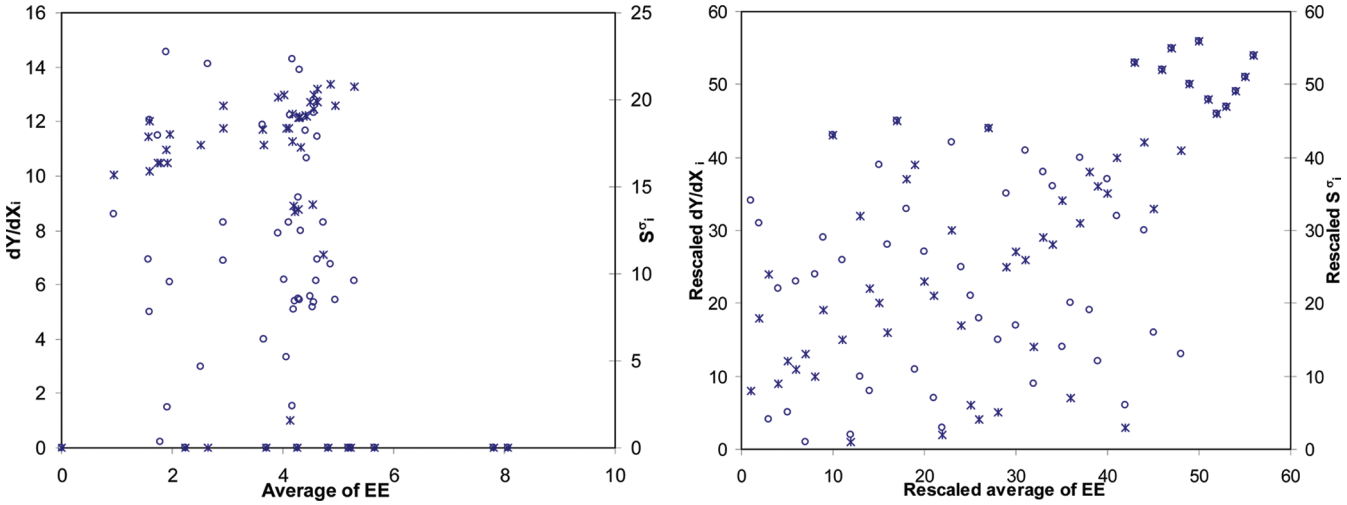


Figure 13. $\partial Y/\partial X_i$ (circles) and S_i^{σ} (stars) versus the screening test, average of the elementary effects. Left panel: logarithmic plots. Right panel: rank-rescaled measures (high importance = high rank; i.e., the most important factor has rescaled measure = 56).

~~motivation for sensitivity analysis in the scientific method, see the last chapter in ref 45. In the present review we discuss two~~ In addition to "factors fixing", another possible objective for sensitivity analysis is~~, i.e.,~~ "factors mapping" and factor importance analysis (see the last chapter in ref 45 for additional objectives), ~~The cut-HDMR is effective for both, as it allows for an efficient though approximate estimate of the~~ f_i ~~terms (mapping), on which a sensitivity measure such as~~ S_i ~~can be computed (importance). At times, the objective of a model-based analysis is to measure~~ which aims at measuring what fraction of the model realizations falls within established bounds or regions, and what factors are responsible for this. This objective can be pursued using a Monte Carlo method known as Monte Carlo filtering (MCF[76−78]). In MCF, one samples the space of the input factors as in the plain MC method and then categorizes the corresponding model output as either within or without the target region (the terms *behavior* (B) or *nonbehavior* (NB) are used). This categorization is then mapped back into the input factors, each of which is thus also partitioned into a behavioral and a nonbehavioral subsample. When the two B, NB samples for a factor are statistically different, then the factor is an influential one. This approach to SA is also known as regionalized sensitivity analysis (RSA). MCF is often used in calibration, as it can successfully point to the existence of alternative behavioral regions in the multidimensional space of the input. In this case, a combination of MCF and variance-based sensitivity analysis of the likelihood (the probability of the data given the model) can be helpful. This and the pros and cons of RSA and its extensions are reviewed in ref 45.

2.10. Meta-Modeling for Sensitivity Analysis

In the 1970s, roughly in the same period when Cukier and co-workers developed FAST, the use of meta-models for sensitivity analysis purposes was pioneered by Blanning and Kleijnen.[50d,e] The effectiveness of meta-modeling depends on the assumption that in eq 27 terms of order higher than two or three are negligible. In several practical cases this is verified, justifying the recent wide development of meta-modeling in the context of sensitivity analysis: kriging[33,69] and Gaussian process models,[50b,c,99] smoothing and nonparametric regressions,[70,70a] polynomial chaos expansions,[71,72] and others.

All meta-models use a MC "training" sample to learn about the mapping between input factors and the model output of interest. Then the estimated meta-model is used to approximate the behavior of the model output for any new input sample, at a much smaller computational cost than the original computational model. Once the appropriate meta-model is generated, model predictions and good sensitivity estimates can be cheaply obtained, in many practical cases also including total effects. Meta-models are recommended when CPU time is very large. They are superior to factorial designs, in that they operate on distributions, not on levels, for the input factors. Note that meta-models can be unsuccessful for particularly nonsmooth models.

In kriging, the analyst needs to implement, e.g., using a Bayesian updating approach, the algorithm to estimate the model itself at "untried" points.[49] The basic assumption of kriging[69,69a] is that training simulation experiments closer to the new point to be predicted should receive more weight. This assumption is formalized through a stationary covariance process with correlations that decrease as the distances between the inputs of observations increase. Moreover, the kriging model is an exact interpolator; i.e., predicted outputs equal simulated outputs at training samples, which is attractive in deterministic simulation. Interpolation, in principle, makes the estimation of kriging emulators very efficient, as confirmed by the many successful applications described in literature, and justifies the great success of this kind of emulator among practitioners. Gaussian process emulation and Bayesian sensitivity analysis[98,99] are special cases of kriging, whereby the latter is put into a strict Bayesian (Gaussian) formulation. More in general, kriging allows more flexible (non-Gaussian) forms for the covariance, as provided by the DACE toolbox.[75a]

Smoothing and nonparametric regressions, as well as polynomial expansions, are also widely used to build meta-models: the main difference with respect to kriging is that these kinds of meta-models are not exact interpolators. Rather, they treat computer experiments assuming a residual or "error" term in their model specification. In practice, these meta-models are built in the form of an ANOVA-HDMR expansion, truncated at second- or third-order terms. Moreover, such an ANOVA expansion is built employing regressor-selection procedures that include only the statistically significant ANOVA terms in the meta-model.[75,75b,75c]

Table 2. Sensitivity Measures for Model (eqs 33−37), As Obtained Using Meta-Models Trained with 512 Model Runs (For Smoothing and Kriging); Results from Sobol' Are the Same as in Table 1

	S_i			S_{Ti}		
	smoothing[75]	kriging[75a]	Sobol'	smoothing[75]	kriging[75a]	Sobol'
ψ	0.2184	0.2142	0.1781	0.6117	0.6651	0.6738
θ_a	0.1594	0.1577	0.1641	0.4253	0.5399	0.556
B	0.0957	0.0949	0.08	0.3846	0.4921	0.4692
γ	0	0.0055	0.0019	0	0.0126	0.0322
θ_i	0	0.000	0.0015	0	0.0031	0.0128
sum	0.4735	0.4722	0.43			

The inclusion of the "error" term, albeit often regarded as a major drawback by the kriging community, turns out to be an advantage in some applications, because it implies that emulation (and therefore "prediction" at new untried sample values) is performed only using statistically significant ANOVA terms, often enhancing the robustness of out-of-sample performances,[75] especially for highly complex models.

An application of ANOVA smoothing splines[75] for the model in eq 2 is shown in Figure 3, together with the Taylor expansion (based on local derivatives at the midpoint) of the same factors. The two model representations are substantially equivalent for this quasi-linear model.

When considering the model (eqs 33−37), meta-modeling displays more clearly its powerful features in providing efficient estimates of sensitivity indices (Table 2) and of ANOVA expansions (Figures 10 and 11). In Table 2 one can see that the main effects are estimated accurately by meta-models when compared to the large sample size Sobol' estimates. Moreover, we can note the key features of the two classes of meta-models. Smoothing does not include in the ANOVA expansion γ and θ_i (their sensitivity indices are zero), reflecting the procedure of component selection: this is a useful property in that the meta-model is built in the most parsimonious way given the available computer experiments. Moreover, when truncating the ANOVA expansion at second-order interactions, total effects turn out to be underestimated, although the sensitivity pattern is still correctly reflected. On the other hand, in this case, kriging is almost able to replicate the entire interaction structure of the model, providing excellent estimates of both main and total effect. Kriging is particularly well-suited for this kind of model, characterized by a small number of input factors. In general, as thoroughly discussed in ref 75, the performance of kriging versus smoothing can be strongly case-dependent, and validation checks can address the users on the most suitable meta-modeling strategy for the problem at hand.

In the present review, we concentrated our attention to the most classical case where the model output of interest is a scalar value. To conclude this short overview of meta-models, we would like to mention new developments that concern the case of distributed model outputs and, in particular, dynamic models. In this latest context, a new class of "dynamic meta-models" has been developed,[100] which aims at reproducing the entire dynamical features of large computational models. This new class of meta-models is suited for a more general and flexible range of applications: data-assimilation and signal processing, control and planning, and engineering system design. In the context of nondynamic models, investigations are ongoing to develop emulators with nonseparable covariance structures.[100a]

3. CONCLUSIONS: WHEN TO USE WHAT

The choice of the proper sensitivity analysis technique can depend upon many factors, including (i) the computational cost of running the model, (ii) the number of input factors, (iii) the degree of complexity of the model coding, (iv) the amount of analyst's time involved in the sensitivity analysis, and (v) the objective of (or the setting for) the analysis (e.g., factors' fixing, mapping,...), see Figure 14.

For models that require a modest amount of CPU time (i.e., up to the order of 1 min per run), and with a number of input factors which does not exceed, say, 20, the class of the variance-based techniques yields the more accurate pattern of sensitivity. Both the method of Sobol' (very easy to code; see, e.g., ref 65c) and the extended FAST (less easy[53]) provide all the pairs of first-order and total indices at a cost of $(k+2)N$ model runs for Sobol' and $\sim kN$ model runs for the extended FAST, where k is the number of factors and N is the number of rows of the matrices **A** and **B** in eq 30. Typically, $N \approx 500-1000$. To give an order of magnitude of the computational requirement, for a model with 10 factors and 0.5 min of CPU time per run, a good characterization of the system via S_i and S_{Ti} can be obtained at the cost of ∼42−84 h of CPU time. Given the greater effort needed to code FAST (and its inadequacy when input factors are sampled from discrete distributions), we would recommend the Sobol' design as implemented in ref 65c for this situation of moderate number of factors and computational time.

What makes this computation expensive is the estimation of the total effect indices S_{Ti}. If one is happy with just estimating the S_i, the cost can be much lower using, e.g., RBD or meta-modeling. Also, when the degree of interactions in the model is not very large, meta-modeling can still be of help in getting useful estimates of S_{Ti} at a smaller cost, provided that the quality of the meta-modeling has been tested.

~~For higher order indices as well as total indices in the case of correlated input, one has to apply a brute force approach whereby the operators V and E (eq 9) are to be written in explicit form (i.e., as the variance of a mean, involving a double computing loop). The computational cost is thus Nr model runs per index.~~

~~All these techniques are implemented in SIMLAB, a free software package.~~

A class of techniques that is attracting increasing attention among practitioners, again for models that require a modest amount of CPU time, and with a number of input factors that does not exceed, say, 12, is that of density-based importance measures, also called moment-independent importance measures.[101] In these techniques, the associated global sensitivity measures explicitly consider the entire model output density instead of relying on a particular moment of this density (e.g., the variance). They are well-suited when output densities are skewed or multimodal, and thus variance cannot completely capture the uncertainty of the model output. An application of this importance measure to the thermal runaway analysis of a batch reactor is also available.[102]

Less expensive alternatives to the variance-based methods are the standardized regression coefficients, SRCs. With a single batch of a

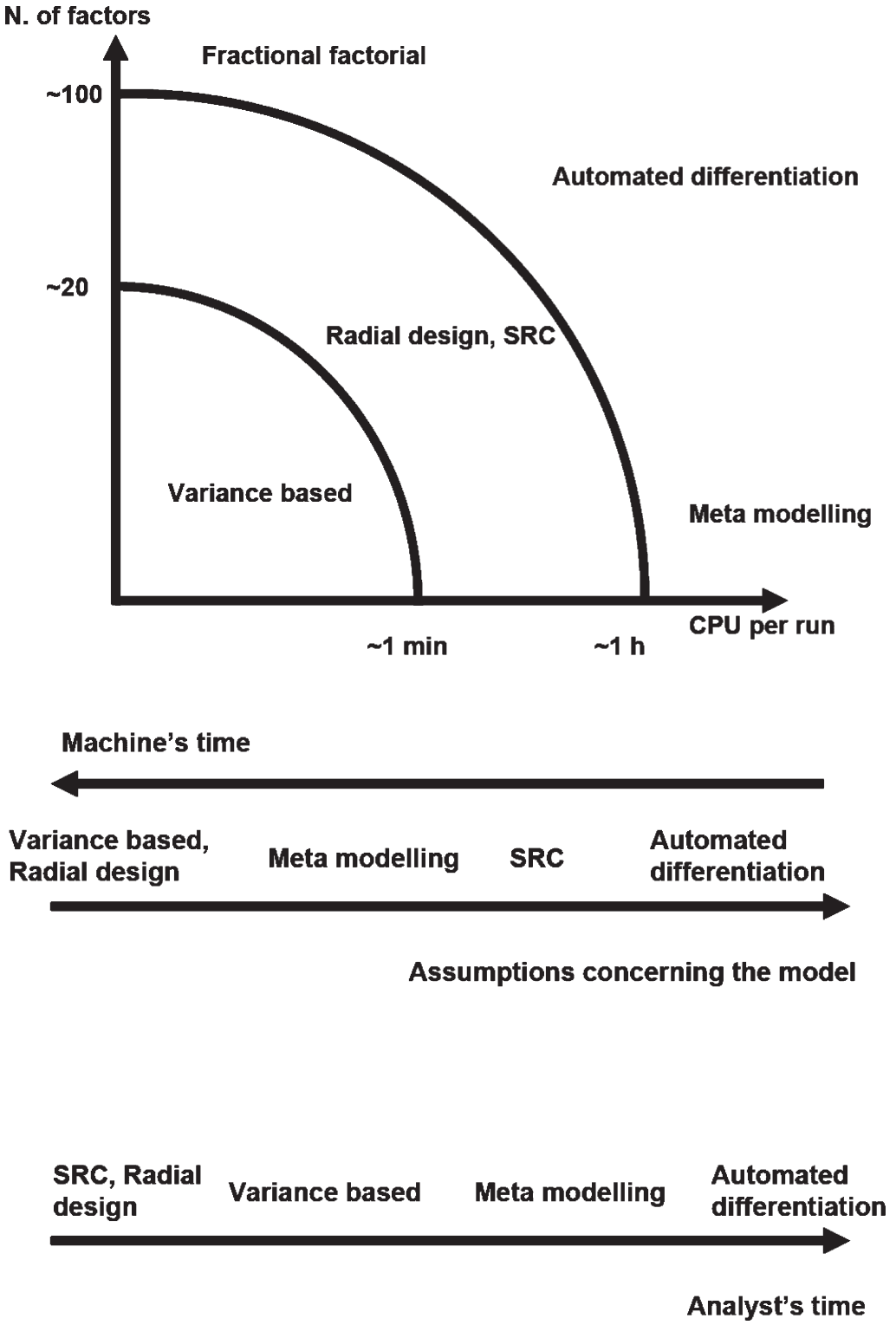


Figure 14. "When to use what". Illustration of the various techniques available and their use in function of computational cost of the model, complexity of the model, dimensionality of the input space, and analyst's time. Note that this is a simplification, e.g., when computing for instance radial screening or S_{Ti}, the sample size, and hence the CPU time, are not independent from the number of variables.

few hundred sampled points (~~say, N ≈ 100 points or less depending on the cost of the model~~), the SRCs and their rank-transformed version can be estimated for all the input factors.

As mentioned, the SRCs are only effective for linear or quasi-linear models, i.e., for high values of R^2. Regression-based sensitivity techniques are often productively coupled with the examination of scatterplots to provide needed insights into nonlinear and possibly interacting effects that lead to regression models with low R^2 values. ~~Regression methods are always useful to be looked at in order to investigate the degree of linearity of~~

dx.doi.org/10.1021/cr200301u |*Chem. Rev.* 2012, 112, PR1–PR21

~~the model and, if regression is not effective,~~ In this latter case, meta-modeling can be applied, using nonparametric smoothing or kriging.

When the CPU time increases (say, up to 10 min per run) or the number of factors increases (say, up to 100), ~~the method of Morris, of which an extension is implemented in SIMLAB,~~ the screening method based on radial sampling described in section 2.8 offers the best result.[51a] Radial sampling requires $N(k + 1)$ points, where k is the number of input factors, and N is in this case set to $N \approx 4-8$ (it was 500−1000 for S_{Ti}). To make an example, with 80 factors and 5 min of CPU time per run, all the model outputs can be ready in 27 h if $N = 4$ is taken. ~~The main drawback of this method is that samples are taken from levels, while both the SRC and the variance-based methods take samples from distributions.~~

A useful practice (ref 51a) would be to start a simulation with a radial design using the estimator for the elementary effect (section 2.8), and then possibly increase the number of points, moving, without waste of simulation points, to the estimator for S_{Ti} (section 2.7). At each number of simulations, a bootstrap[68,65c] procedure can be used to estimate the confidence bounds on the sensitivity indices.

Automatic differentiation techniques[3] can also be used when CPU time is very large. They are inherently local. In addition, they require intervention of the analyst in the computer code that implements the model. However, for expensive models, these methods may offer an approximate solution for factors importance assessment and are very informative for factors mapping, as well as for data assimilation applications.[17] If higher order derivatives are computed,[16] these give information about multifactor curvature effects and could be seen as a bridge between local and global methods; e.g., a second-order term of the type $\partial^2 Y/\partial X_i \partial X_j$ gives information about a possible interaction effect between X_i and X_j, although the S_{ij} variance-based measure will include an element of averaging over the entire space of the factors. The advantages of higher order (second, third) local sensitivity analysis in the presence of nonlinear outputs (e.g., an ozone peak concentration) are discussed in ref 19. In a Taylor-expansion framework, higher order terms allow a better exploration further away from the baseline. According to ref 14, while first-order sensitivities can predict ozone concentration at about a 25% factors variation away from their baseline, with second-order terms the prediction is good up to 50% variations away from the baseline values.

As an alternative, a Monte Carlo based approach to estimation has also been tried in chemistry, which includes a quantitative sensitivity analysis step.[45,90,91]

Sensitivity analysis is also driven by the setting.[45] When the purpose of the analysis is to prioritize factors, the first-order sensitivity indices S_i are a natural choice. If the objective is to fix noninfluential factors, then the total sensitivity indices S_{Ti}, or (if the model is expensive) ~~the measure of Morris~~ screening, come into use. If a particular region in the space of the output (e.g., above or below a given threshold) is of interest, then Monte Carlo filtering and associated methods can be tried as an alternative or complement to the measures just mentioned. If the purpose of the analysis is a diagnostic mapping of the input/output relationship, then various estimates of functional decomposition (eq 27) can be tested (see Figures 10 and 11). At all of these settings, the computation of derivatives, especially if achieved with a modicum of extra computing, is advisable for a general understanding of the model.

~~4. Other Methods and Ongoing Research. In Bayesian sensitivity analysis, the analyst needs to implement, by Bayesian updating, the algorithm to estimate the model itself at "untried" points. Once the appropriate sample is generated, model values and good estimates of S_i can be very cheaply generated. Bayesian methods can be recommended when CPU time is very large. They are superior to factorial designs, in that they operate on distributions, not on levels, for the input factors. Note that the Bayesian approach can be unsuccessful for particularly stiff models.~~

~~Approaches that demand extensive analysis of the model also require that the model remains stable in time, as each model revision, especially in the Bayesian approach, will call for a new analysis of the model prior to sensitivity calculation.~~

~~Present research in sensitivity analysis focuses on how to accelerate the computation of the sensitivity indices (S_i and higher order). The Bayesian method already cited is a possible avenue, as well as the cut-HDMR-based approach illustrated in Figure 10. Another strategy, easier to code, is based on random balance designs and uses Fourier analysis to estimate all the first-order indices at a total cost of N model runs (i.e., the same cost of SRCs). State-dependent parameter (SDP) modeling, a nonparametric model estimation approach based on recursive filtering and smoothing estimation, is also being applied successfully to produce both the ANOVA-HDMR f_i terms and the relative S_i at the same cost of SRCs.~~

AUTHOR INFORMATION

Corresponding Author

*Telephone: +39 0332 789686. Fax: +39 0332 785733. E-mail: andrea.saltelli@jrc.ec.europa.eu.

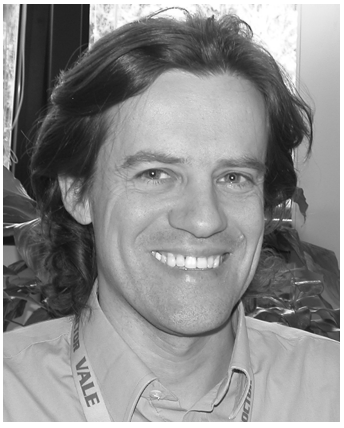
The authors declare no competing financial interest.

BIOGRAPHIES

Andrea Saltelli, born in 1953, graduated in Chemistry in 1976, first of his course, with two awards. He coauthored 4 books and about 80 articles in disciplinary journals over the last 35 years, on topics from Chemistry to Environmental Sciences to Applied Statistics and Econometrics. His main research interest is in sensitivity analysis, also in relation to impact assessment studies. Another focus of his research is the construction of composite indicators. Presently, he leads the Econometric and Applied Statistics Unit of the Joint Research Centre in Ispra. The Unit, with a staff of 30, develops models,

indicators, and econometric−statistic applications in support to the services of the European Commission. Andrea Saltelli is active in the organization of international courses and summer schools on sensitivity analysis (SAMO series) and composite indicators.

Marco Ratto, born in 1970, graduated in Chemical Engineering from the University of Genova in 1994. He received his Ph.D. in Chemical Engineering in 1998. Since 2000, he has been working at the Joint Research Centre of the European Commission. His main research interests concern modeling, simulation, and estimation; global sensitivity and uncertainty analysis; and nonlinear dynamics, in a variety of applied disciplines—from chemical and process engineering systems, to environmental sciences, to macroeconomic modeling. He is author of over 30 papers in peer review journals and coauthor of two books on sensitivity analysis.



Stefano Tarantola, born in 1967, is a Scientific Officer of the Joint Research Centre of the European Commission, who graduated in Engineering in 1992 and received his Ph.D. in Science and Technologies for engineering from the Polytechnic of Milan in 1996. He carries out and coordinates scientific R&D tasks in the field of innovation indicators. He conducts statistical work on indicators and composite indicators for the Innovation Union flagship. He has experience in systems analysis and Monte Carlo, quasi-Monte Carlo simulation modeling. He combines sensitivity analysis and participatory methods for the construction of composite indicators and develops methodologies for sensitivity analysis. He is author of papers in the peer reviewed literature, coauthor of 4 books on sensitivity analysis, and organizer of training courses and conferences on sensitivity analysis of model output (SAMO).

Francesca Campolongo, born in 1970, graduated in Applied Mathematics from the University of Pisa, Italy, in 1993. In 1998, she completed her Ph.D. in modeling and sensitivity analysis at the Faculty of Environmental Sciences of Griffith University, QLD, Australia. Two Australian scholarships, OPRS and GUPRS, covered her Ph.D. In 1995 she was selected to participate in a 1-month summer school on ecological modeling at Cornell University (Ithaca, NY). Since March 1998, she has been working at the Joint Research Centre of the European Commission (Ispra, Italy), where she also obtained in 2002 a prize as "best JRC young scientist of the year". Her main research interests focus on modeling, uncertainty and sensitivity analysis, and risk assessment, applied to a variety of settings. During her Ph.D. and postdoctoral studies, she focused on environmental problems, with specific attention to the climate change issue. Since March 2000, she has developed expertise in the field of financial mathematics and financial risk analysis. She has over 20 scientific publications on refereed journals and is coauthor of 2 books on sensitivity analysis published by John Wiley & Sons.

ACKNOWLEDGMENT

Paola Annoni and Andrea Pagano (same affiliation as the authors) have provided useful comments for the present perennial review.

REFERENCES

(1) Rosen, R. *A Comprehensive Inquiry into the Nature, Origin, and Fabrication of Life*; Columbia University Press: New York, 1991.

(2) *Sensitivity Analysis*; Saltelli, A., Chan, K., Scott, M., Eds.; John Wiley & Sons: Chichester, 2000. (a) Saltelli, A.; Ratto, M.; Andres, T.; Campolongo, F.; Cariboni, J.; Gatelli, D.; Saisana, M.; Tarantola, S. *Global Sensitivity Analysis. The Primer*; John Wiley & Sons: Chichester, 2008.

(3) Grievank, A. In *Evaluating derivatives, Principles and techniques of algorithmic differentiation*; SIAM, 2000. (a) Bischof, C.; Carle, A.; Corliss, G.; Griewank, A.; Hovland, P. ADIFOR—Generating Derivative Codes from Fortran Programs. *Scientific Programming*; 1992; Vol. 1, pp 1−29.

(4) Turányi, T. *J. Math. Chem.* **1990**, *5*, 203.

(5) Rabitz, H.; Kramer, M.; Dacol, D. *Annu. Rev. Phys. Chem.* **1983**, *34*, 419.

(6) Rabitz, H. *Science* **1989**, *246*, 221.

(7) Tomlin, A. S.; Turányi, T. In *Low-temperature Combustion and Autoignition*; Pilling, M. J., Hancock, G., Eds.; Elsevier: 1997; p 293.

(8) Varma, A.; Morbidelli, M.; Wu, H. *Parametric Sensitivity in Chemical Systems*; Cambridge: 1999.

(9) Turányi, T.; Rabitz, H. In *Sensitivity Analysis*; Chan, K., Scott, M., Eds.; John Wiley & Sons: Chichester, 2000; p 81.

(10) Cacuci, D. G. In *Sensitivity & Uncertainty Analysis, Vol. 1: Theory*; Chapman & Hall: 2003. (a) Cacuci, D. G., Ionescu-Bujor, M. In *Handbook of Nuclear Engineering, Vol. 3*; Springer: 2010.
(11) Ionesco-Bujor, M.; Cacuci, D. G. *Nucl. Sci. Eng.* **2004**, *147*, 189. (a) Loeppky, J. L.; Sacks, J.; Welch, W. *Technometrics* **2004**, *51*, 366.
(12) Saltelli, A.; Hjorth, J. *J. Atmos. Chem.* **1995**, *21*, 187.
(13) Pandis, S. N.; Seinfeld, J. H. *J. Geophys. Res.* **1989**, *94*, 1105.
(14) Vuilieumier, L.; Harley, R.; Brown, N. J. *Environ. Sci. Technol.* **1997**, *31*, 1206.
(15) Kioutsioukis, I.; Melas, D.; Zerefos, C.; Ziomas, I. *Comput. Phys. Commun.* **2005**, *167*, 23.
(16) Le Dimet, F.-X.; Navon, I. M.; Daescu, D. N. *Mon. Weather Rev.* **2002**, *130*, 629. (a) Saltelli, A.; Annoni, P. *Environ. Modell. Soft.* **2010**, *25*, 1508.
(17) Mallet, V.; Sportisse, B. *Atmos. Chem. Phys. Discuss.* **2004**, *4*, 1371.
(18) Saltelli, A. *J. Geophys. Res.* **1999**, *104*, 3789. **1999**, *104*, 24013. (a) Sobol', I. M.; Kucherenko, S. *Math. Comput. Simul.* **2009**, *79*, 3009. (b) Sobol', I. M.; Kucherenko, S. *Comput. Phys. Commun.* **2010**, *181*, 1212.
(19) Hakami, A.; Odman, M. T.; Russel, A. G. *Environ. Sci. Technol.* **2003**, *37*, 2442.
(20) Cukier, R. I.; Fortuin, C. M.; Shuler, K. E.; Petschek, A. G.; Schaibly, J. H. *J. Chem. Phys.* **1973**, *59*, 3873.
(21) Schaibly, J. H.; Shuler, K. E. *J. Chem. Phys.* **1973**, *59*, 3879.
(22) Cukier, R. I.; Schaibly, J. H.; Shuler, K. E. *J. Chem. Phys.* **1975**, *63*, 1140.
(23) Cukier, R. I.; Levine, H. B.; Shuler, K. E. *J. Comput. Phys.* **1978**, *26*, 1.
(24) Pierce, T. H.; Cukier, R. I. *J. Comput. Phys.* **1981**, *41*, 427.
(25) Koda, M.; McRae, G. J.; Seinfeld, J. H. *Int. J. Chem. Kinet.* **1979**, *11*, 427.
(26) McRae, G. J.; Tilden, J. W.; Seinfeld, J. H. *Comput. Chem. Eng.* **1982**, *6*, 15.
(27) Koda, M.; Dogru, A. H.; Seinfeld, J. H. *J. Comput. Phys.* **1979**, *30*, 259.
(28) Koda, M. *Atmos. Environ.* **1982**, *16*, 2595.
(29) Koda, M.; Seinfeld, J. H. *IEEE Trans. Autom. Control* **1982**, *27*, 951.
(30) Liepmann, D.; Stephanopoulos, G. *Ecol. Modell.* **1985**, *30*, 13.
(31) Helton, J. C. *Reliab. Eng. Syst. Saf.* **1993**, *42*, 327.
(32) Saltelli, A.; Tarantola, S.; Campolongo, F. *Stat. Sci.* **2000**, *15*, 377.
(33) Santner, T. J.; Williams, B. J.; Notz, W. I. *Design and Analysis of Computer Experiments*; Springer-Verlag: 2003.
(34) Helton, J. C.; Davis, F. J. *Reliab. Eng. Syst. Saf.* **2003**, *81*, 23.
(35) Cacuci, D. G.; Ionesco-Bujor, M. *Nucl. Sci. Eng.* **2004**, *147*, 204.
(36) Goldsmith, C. H. In *Encyclopaedia of Biostatistics*; Armitage, P., Colton, T., Eds.; Wiley: New York, 1998. (a) Xu, C.; Gertner, G. *Comp. Stat. Data Anal.* **2011**, *55* (2011), 184.
(37) Hora, S. C.; Iman, R. L. *Sandia Lab. Rep.* **1986**, SAND85–2839.
(38) Ishigami, T.; Homma, T. In *Proceedings of the ISUMA '90*, First International Symposium on Uncertainty Modelling and Analysis; University of Maryland: December 3−5, 1990; p 398.
(39) Iman, R. L.; Hora, S. C. *Risk Anal.* **1990**, *10*, 401.
(40) Krzykacz-Hausmann, B. Technical Report GRS-A-1700; Gesellschaft fuer Reaktor Sicherheit (GRS) MbH: Garching, 1990.
(41) Saltelli, A.; Andres, T. H.; Homma, T. *Comput. Stat. Data Anal.* **1993**, *15*, 211.
(42) Sobol', I. M. *Math. Modell. Comput. Exp. (Engl. Transl.)* **1993**, *1*, 407.
(43) Homma, T.; Saltelli, A. *Reliab. Eng. Syst. Saf.* **1996**, *52*, 1.
(44) McKay, M. D. *LA-UR-96-2695* **1996**, 1.
(45) Saltelli, A.; Tarantola, S.; Campolongo, F.; Ratto, M. *Sensitivity Analysis in Practice. A Guide to Assessing Scientific Models*; John Wiley & Sons Publishers: New York, 2004.
(46) Rabitz, H.; Aliş, Ö. F.; Shorter, J.; Shim, K. *Comput. Phys. Commun.* **1999**, *117*, 11.
(47) Rabitz, H.; Aliş, Ö. F. In *Sensitivity Analysis*; Chan, K., Scott, M., Eds.; John Wiley & Sons: Chichester, 2000; p 199. (a) Li, G.; Rabitz, H.; Yelvington, P. E.; Oluwole, O. O.; Bacon, F.; Kolb, C. E; Schoendorf, J. *J. Phys. Chem.* **2010**, *114A*, 6022. (b) Brell, G.; Li, G.; Rabitz, H. *J. Chem. Phys.* **2010**, *132*, 174103.
(48) Box, G. E. P.; Hunter, W. G.; Hunter, J. S. *Statistics for experimenters*; John Wiley and Sons: New York, 1978.
(49) Sacks, J.; Welch, W. J.; Mitchell, T. J.; Wynn, H. P. *Stat. Sci.* **1989**, *4*, 409. (a) Devon Lin, C.; Bingham, D.; Sitter, R. R.; Tang, B. *Ann. Stat.* **2010**, *38*, 1460.
(50) Welch, W. J.; Buck, R. J.; Sacks, J.; Wynn, H. P.; Mitchell, T. J.; Morris, M. D. *Technometrics* **1992**, *34*, 15. (a) MUCM, Managing Uncertainty in Complex Models; see project's website, www.mucm.ac.uk. (b) O'Hagan, A. *Reliab. Eng. Syst. Saf.* **2006**, *91*, 1290. (c) Kennedy, M. C.; Anderson, C. W.; Conti, S.; O'Hagan, A. *Reliab. Eng. Syst. Saf.* **2006**, *91*, 1301. (d) Blanning, R. *Simulation* **1975**, *24*, 177. (e) Kleijnen, J. *Interfaces* **1975**, *5*, 21.
(51) Morris, M. D. *Technometrics* **1991**, *33*, 161. (a) Campolongo, F.; Saltelli, A.; Cariboni, J. *Comput. Phys. Commun.* **2011**, *182* (4), 978.
(52) Saltelli, A.; Bolado, R. *Comput. Stat. Data Anal.* **1998**, *26*, 445.
(53) Saltelli, A.; Tarantola, S.; Chan, K. *Technometrics* **1999**, *41*, 39.
(54) Saltelli, A.; Tarantola, S. *J. Am. Stat. Assoc.* **2002**, *97*, 702.
(55) Hamby, D. M. *Environ. Monit. Assess.* **1994**, *32*, 135.
(56) Kleijnen, J. P. C. In *Handbook of Simulation*; Banks, J., Ed.; Wiley: New York, 1998.
(57) Frey, H. C., Ed. *Risk Anal.* **2002**, 22.
(58) Chance, E.; Curtis, A.; Jones, I.; Kirby, C. Report AERE-B8775; Harwell: 1977.
(59) http://www.reactiondesign.com/; see also CHEMKIN page at SANDIA Labs. http://www.ca.sandia.gov/chemkin/.
(60) Turányi, T.; Zalotai, L.; Dóbé, S.; Bercé, T. *Phys. Chem. Chem. Phys.* **2002**, *4*, 2568.
(61) Kleijnen, J. P.; Helton, J. C. *Reliab. Eng. Syst. Saf.* **1999**, *65*, 147.
(62) Draper, N. R.; Smith, H. *Applied Regression Analysis*; John Wiley & Sons: New York, 1981.
(63) Campolongo, F.; Saltelli, A.; Jensen, N. R.; Wilson, J.; Hjorth, J. *J. Atmos. Chem.* **1999**, *32*, 327.
(64) Iman, R. L.; Conover, W. J. *Technometrics* **1979**, *21*, 499. (a) Helton, J. C.; Johnson, J. D.; Sallaberry, C. J.; Storlie, C. B. *Reliab. Eng. Syst. Saf.* **2006**, *91*, 1175.
(65) Saltelli, A.; Sobol', I. M. *Reliab. Eng. Syst. Saf.* **1995**, *50*, 225. (a) Efron, B.; Tibshirani, R. J. *An introduction to the bootstrap*; Chapman & Hall: New York, 1993. (b) Pearson, K. On the General Theory of Skew Correlation and Non-linear Regression. *Mathematical Contributions to the Theory of Evolution, Drapers' Company Research Memoirs*, Vol. XIV; Dulau & Co.: London, 1905. Reprinted in: *Early Statistical Papers*; Cambridge University Press: Cambridge, U.K., 1948. (c) Saltelli, A; Annoni, P; Azzini, I; Campolongo, F; Ratto, M; Tarantola, S. *Comput. Phys. Commun.* **2010**, *181*, 259. (d) Mara, T. *Reliab. Eng. Syst. Saf.* **2009**, *94*, 1274. (e) Kucherenko, S.; Tarantola, S.; Annoni, P. *Comput. Phys. Commun.* **2012**, *183*, 937.
(66) Tarantola, S.; Gatelli, D.; Mara, T. *Reliab. Eng. Syst. Saf.* **2006**, *91*, 717.
(67) Chan, K.; Tarantola, S.; Saltelli, A.; Sobol', I. M. In *Sensitivity Analysis*; Saltelli, A., Chan, K., Scott, M., Eds.; John Wiley & Sons: Chichester, 2000; p 167.
(68) Archer, G.; Saltelli, A.; Sobol', I. M. *J. Stat. Comput. Simul.* **1997**, *58*, 99.
(69) Kleijnen, J. *Eur. J. Oper. Res.* **2009**, *192*, 707. (a) Jones, D. R.; Schonlau, M.; Welch, W. J. *J. Global Optim.* **1998**, *13*, 455.
(70) Storlie, C. B.; Swiler, L. P.; Helton, J. C.; Sallaberry, C. J. *Reliab. Eng. Syst. Saf.* **2009**, *94*, 1735. (a) Storlie, C. B.; Helton, J. C. *Reliab. Eng. Syst. Saf.* **2008**, *93*, 28. (b) Storlie, C. B.; Helton, J. C. *Reliab. Eng. Syst. Saf.* **2008**, *93*, 55.
(71) Sudret, B. *Reliab. Eng. Syst. Saf.* **2008**, *93*, 964.
(72) Crestaux, T.; Le Maitre, O.; Martinez, J.-M. *Reliab. Eng. Syst. Saf.* **2009**, *94*, 1161.
(73) Morbidelli, M.; Varma, A. *Chem. Eng. Sci.* **1988**, *43*, 91.

(74) Saltelli, A. *Comput. Phys. Commun.* **2002**, *145*, 280.
(75) Ratto, M.; Pagano, A. *Adv. Stat. Anal.* **2010**, *94*, 367. (a) Lophaven, S.; Nielsen, H.; Sondergaard, J. DACE A MATLAB kriging toolbox, Version 2.0. Technical Report IMM-TR-2002-12; *Informatics and Mathematical Modelling*; Technical University of Denmark: 2002. (b) Storlie, C. B.; Bondell, H. D.; Reich, B. J.; Zhang, H. H. *Stat. Sin.* **2011**, *21*, 679. (c) Ratto, M.; Pagano, A.; Young, P. *Comput. Phys. Commun.* **2007**, *177*, 863.
(76) Hornberger, G. M.; Spear, R. C. *J. Environ. Manage.* **1981**, *12*, 7.
(77) Young, P. C.; Parkinson, S. D.; Lees, M. *J. Appl. Stat.* **1996**, *23*, 165.
(78) Young, P. *Comput. Phys. Commun.* **1999**, *117*, 113.
(79) Krzykacz-Hausmann, B. In *Proceedings of SAMO2001*; Prado, P., Bolado, R., Eds.; CIEMAT: Madrid, 2001; p 31.
(80) Campolongo, F.; Kleijnen, J.; Andres, T. In *Sensitivity Analysis*; Saltelli, A., Chan, K., Scott, M.; John Wiley & Sons: Chichester, 2000; p 65.
(81) Capaldo, K. P.; Pandis, S. N. *J. Geophys. Res.* **1997**, *102*, 23/251.
(82) Campolongo, F.; Tarantola, S.; Saltelli, A. *Comput. Phys. Commun.* **1999**, *117*, 75. (a) Boukouvalas, A.; Gosling, J. P.; Maruri-Aguilar, H. An efficient screening method for computer experiments, Technical report; Aston University: Birmingham, U.K., February 2010.
(83) Le Bras, G.; Barneş, I.; Hjorth, J.; Zetzsch, C.; Martinez, E.; Mihalopoulos, N. *Report EUR 19569 EN*; European Commission: Luxembourg, 2000.
(84) Sobol', I. M. *USSR Comput. Math. Math. Phys.* **1976**, *16* (5), 1332.
(85) Bratley, P.; Bennet, L. F. *ACM Trans. Math. Software* **1988**, *14*, 88.
(86) Iman, R. L.; Conover, W. J. *Commun. Stat.: Theory Methods* **1980**, *A9*, 1749. (a) Kucherenko, S.; Rodriguez-Fernandez, M.; Pantelides, C.; Shah, N. *Reliab. Eng. Syst. Saf.* **2009**, *94*, 1135.
(87) McKay, M. D.; Beckman, R. J.; Conover, W. J. *Technometrics* **1979**, *21*, 239.
(88) McKay, M. D. Technical Report NUREG/CR-6311, LA-12915-MS; U.S. Nuclear Regulatory Commission and Los Alamos National Laboratory: 1995. (a) Xu, C.; Gertner, G. Z. *Reliab. Eng. Syst. Saf.* **2008**, *93*, 1060.
(89) http://sensitivity-analysis.jrc.ec.europa.eu/. This site maintained by the authors at the Joint Research Centre of the European Commission contains tutorials, software, quasi-random number generators, and test functions for sensitivity analysis.
(90) Ratto, M.; Tarantola, S.; Saltelli, A. *Comput. Phys. Commun.* **2001**, *136*, 212.
(91) Scire, J. J.; Dryer, F. L.; Yetter, R. A. *Int. J. Chem. Kinet.* **2001**, *33*, 784.
(92) KINALC is freely available at http://www.chem.leeds.ac.uk/Combustion/kinalc.htm. See also:Turányi, T. *Comput. Chem.* **1990**, *14*, 253 .
(93) Scott, M., Saltelli, A., Eds. *J. Stat. Comput. Simul.* **1997**, 57.
(94) Saltelli, A., Chan, K., Scott, M., Eds. *Comput. Phys. Commun.* **1999**, 117.
(95) Tarantola, S., Saltelli, A., Eds. *Reliab. Eng. Syst. Saf.* **2003**, 79.
(96) Helton, J. C.; Cooke, R.; McKay, M. D.; Saltelli, A., Eds. *Reliab. Eng. Syst. Saf.* **2006**, *91*, 1105.
(97) Cawlfield, J. D. In *Sensitivity Analysis*; Saltelli, A., Chan, K., Scott, M., Eds.; John Wiley & Sons: Chichester, 2000; p 155.
(98) O'Hagan, A.; Kennedy, M. C.; Oakley, J. E. *Bayesian Stat.* **1999**, *6*, 503.
(99) Oakley, J.; O'Hagan, A. *J. R. Stat. Soc., Ser. B* **2004**, *66*, 751.
(100) Young, P. C.; Ratto, M. *Technometrics* **2011**, *53*, 29. (a) Fricker, T. E.; Oakley, J. E.; Sims, N. D.; Worden, K. *Mech. Syst. Signal Proc.* **2011**, *25*, 2962.
(101) Borgonovo, E. *Reliab. Eng. Syst. Saf.* **2007**, *92*, 771.
(102) Borgonovo, E.; Tarantola, S. *Int. J. Chem. Kinet.* **2008**, *40*, 687.
(103) Marino, S.; Hogue, I. B.; Ray, C. J.; Kirschner, D. E. *J. Theor. Biol.* **2008**, *254* (1), 178.