SOP for global sensitivity analysis of dynamic models of biochemical systems

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1 Motivations and Objectives

The standard operating procedure (SOP) for applying the most widely used[1] local and global sensitivity analysis methods is described here. They can be used for detecting non influential parameters and, some of them, also their interactions in non linear dynamical models. Moreover, a parameter ranking based on these measures can be established which allows the prioritization of parameters that can be subsequently estimated using robust global optimization methods [2].

2 Sensitivity analysis methods

Local sensitivities provide the slope of the calculated model output in the parameter space at a given set of nominal values considered for the parameters so the behavior of the response function is described only locally in the input space. Moreover, preliminary experiments and model calibration tests should be carried out in order to obtain a first guess for the parameter values and an iterative scheme involving both steps is required in order to study the model sensitivity. In addition, these methods are linear thus they are not sufficient for dealing with complex models, especially those in which there are nonlinear interactions between parameters.

In contrast, global sensitivity analysis (GSA) methods evaluate the effect of a parameter while all other parameters are varied simultaneously, thus accounting for interactions between parameters without depending on the stipulation of a nominal point (they explore the entire range of each parameter). The most widely used methods in GSA are FAST and extended FAST, the Morris method and its adaptations and the Sobol' method [3] considered as one of the more powerful despite its high computational cost.

2.1 Numerical methods for the calculation of local sensitivity indices

Local sensitivity coefficients are the partial derivatives of the model state variables to the model parameters evaluated at the normal operating point where all the parameters have their nominal values.

Considering the case of ODEs, a popular statement is the so-called state-space formulation:

$$\dot{x}(p,t) = f[x(p,t), u(t), p],\ x(0) = x_0, \tag{1}$$

$$y(p,t) = g[x(p,t), u(p,t), p] \tag{2}$$

where x is the vector of N_x state variables and p the vector of n model parameters. Note that f specify the model, u specifies the vector of inputs (i.e. for a particular experiment) and y the vector of N_y measured states. An experiment is specified by the initial conditions $x(0)$, the inputs u chosen among a set of possible inputs U and the observations y. Note that the inputs can be time-dependent. Then the sensitivity coefficients of the measured states that form the sensitivity matrix are:

$$E_{i,j} = \left(\frac{\partial y_j}{\partial p_i}\right)_{y=y(t,\hat{p}),p=\hat{p}} \tag{3}$$

They are several numerical methods for calculating the local sensitivity indices although the computed values should be the same among the precision of the considered method. The decoupled direct method (DDM) has proven to be the best general method for the numerical calculation of local sensitivities [4]. One of the best known implementations of this method is ODESSA, a package of FORTRAN routines for simultaneous solution of ordinary differential equations and the associated fist-order parametric sensitivity equations, developed by [5]. ODESSA is a modification of the initial-value solver LSODE, and is the one recommended in this SOP.

Absolute sensitivity functions (Eq. 3) are useful for calculating errors due to parameter variations and for assessing the times at which a parameter has its greatest or least effect. However, absolute sensitivity functions are not normalized and they are not useful for comparing the effects of different parameters with respect to different states, for what we should use relative-sensitivity functions.

The relative sensitivity of the state y_j to variations in the parameter p_i is given by:

$$E^r_{i,j} = \frac{\%\ change\ in\ p_i}{\%\ change\ in\ y_j} = \frac{\partial y_j / y_j}{\partial p_i / p_i} = \frac{p_i}{y_j}\left(\frac{\partial y_j}{\partial p_i}\right)_{y=y(t,\hat{p}),p=\hat{p}} \tag{4}$$

Relative sensitivity functions are formed by multiplying the partial derivative (the absolute sensitivity function) by the nominal value of the parameter and dividing by the value of the function. They are ideal for comparing parameters, because they are dimensionless, normalized functions. However, the relative-sensitivity function presents division by zero problems when y_j is equal to zero and gives undue weight to the response if it is small.

2.2 Sobol' global sensitivity indices

The method of global sensitivity indices developed by Sobol' is the most established among the variance-based methods. The method is based on the ANOVA decomposition of the variance of the model output. A detailed description of the method can be found in [6].

Sobol' define two type of indices: SI_i that accounts only for the effect of the parameters p_i and SI^T_i that also accounts for the interactions of the parameter p_i with the rest of the parameters. He found a elegant way of computing these indices directly from the model output $y_j(p)$ being $\bar{p_i}$ the set of parameters excluding p_i:

$$SI_{i,j} = \frac{\int_{H^n} y_j(p_i, \bar{p}_i) y_j(p_i, \bar{p}_i{}') dp_i d\bar{p}_i d\bar{p}_i{}' - y^2_{j,0}(p)}{\int_{H^n} y^2_j(p) dp - y^2_{j,0}(p)} \tag{5}$$

$$SI^T_{i,j} = \frac{1}{2} \frac{\int_{H^n} \left[y_j(p_i, \bar{p}_i) y_j(p'_i, \bar{p}_i)\right]^2 dp_i dp'_i d\bar{p}_i}{\int_{H^n} y^2_j(p) dp - y^2_{j,0}(p)} \tag{6}$$

Using these indices a parameter ranking can be established.

2.3 Derivative based Global Sensitivity Measures

Kucherenko and co-workers [7] presented the derivative based global sensitivity measures (DGSM) based on averaging local derivatives using Quasi Monte Carlo sampling methods. They applied this technique to a set of explicit functions showing that it is much more accurate than the Morris

method. Moreover, they demonstrated that there is a link between these measures and the Sobol' sensitivity indices.

In [8], these measures were extended in order to be able to handle ordinary differential equations (ODEs). The details of this methodology are described below.

Consider a model described by a set of ODEs, $f(p)$, where $p = \{p_i\}$ is a vector of parameters defined in the unit hypercube H^n ($0 \leq p_i \leq 1, i = 1, ..., n$). Local sensitivity measures are based on the partial derivatives of the states y_j (3). Sensitivity measures $E_{i,j}(p^*)$ depend on a nominal point and they change with a change of p^*. This deficiency can be overcome by averaging $E_{i,j}(p^*)$ over the parameter space H^n. Such a measure can be defined as:

$$\bar{M}_{i,j} = \int_{H^n} E_{i,j} dp \tag{7}$$

Another measure, which is the variance of $\bar{M}_{i,j}$, is also considered

$$\bar{\Sigma}_{i,j} = \left[\int_{H^n} \left(E_{i,j} - \bar{M}_{i,j} \right)^2 dp \right]^{1/2} \tag{8}$$

$\bar{\Sigma}_{i,j}$ can also be presented as

$$\bar{\Sigma}^2_{i,j} = \int_{H^n} E^2_{i,j} dp - \bar{M}^2_{i,j} \tag{9}$$

Combining $\bar{M}_{i,j}$ and $\bar{\Sigma}_{i,j}$ a new measure $\bar{G}_{i,j}$ can be introduced

$$\bar{G}_{i,j} = \bar{\Sigma}^2_{i,j} + \bar{M}^2_{i,j} = \int_{H^n} E^2_{i,j} dp \tag{10}$$

For a single parameter p_i or a number of parameters b in a subset we can define the so called "alternative global sensitivity estimator", $\bar{G}^a_b$, as

$$\bar{G}^a_{b,j} = \frac{\sum_{i=1}^{b} \bar{G_{i,j}}}{\sum_{i=1}^{n} \bar{G_{i,j}}} \tag{11}$$

The main advantage of this index is that it is able to handle groups of parameters and that it is normalized between zero and one allowing to compare the sensitivity of a parameter with respect to different outputs.

Non-monotonic functions have regions of positive and negative values of partial derivatives $E_{i,j}(p^*)$, hence due to the effect of averaging values $\bar{M}_{i,j}$

can be very small or even zero: i.e. for a symmetrical at a middle point ($p = 0.5$) function $\bar{M}_{i,j} = 0$. To avoid such situations measures based on the absolute value of $|E_{i,j}(p^*)|$ can be used:

$$\bar{M}^*_{i,j} = \int_{H^n} |E_{i,j}|\, dp \tag{12}$$

$$\bar{\Sigma}^*_{i,j} = \left[\int_{H^n} \left(|E_{i,j}| - \bar{M}^*_{i,j}\right)^2 dp\right]^{1/2} \tag{13}$$

Similar measures were introduced in [9] within the framework of the Morris method. $\bar{G}^a_{i,j}$ does not present this problem since it is the result of the integration of the squared local sensitivity over the parameter space. Using an analogy with variance based global sensitivity measures, the set of measures $\bar{M}^*_{i,j}$, $\bar{\Sigma}^*_{i,j}$ and $\bar{G}^a_{i,j}$ are called derivative based global sensitivity measures (DGSM).

It has been concluded in [7] that $\bar{G}^a_{i,j}$ is a better proxy for $SI^T_{i,j}$ than $\bar{M}^*_{i,j}$, so this is the measure recommended for the ranking of parameters.

2.4 Computational algorithms for calculation of integrals

Calculation of Sobol' indices and DGSM is based on the evaluation of a series of integrals (those involved in Eq. (5-6) and Eq. (11) respectively) that can be presented in the following generic form:

$$I\,[f] = \int_{H^n} f(p) dp \tag{14}$$

It is assumed that function $f(p)$ is integrable in the n-dimensional unit hypercube H^n.

Classical grid methods become inefficient in high-dimensions because of the "curse of dimensionality" (exponential grows of the required integrand evaluations). Monte Carlo methods do not depend on the dimensionality and are effective in high dimensional integrations. However, the efficiency of MC methods is determined by the properties of random numbers. It is known that random number sampling is prone to clustering: for any sampling there are always empty areas as well as regions in which random points are wasted due to clustering. As new points are added randomly, they do not necessarily fill the gaps between already sampled points.

A higher rate of convergence can be obtained by using deterministic uniformly distributed sequences also known as low-discrepancy sequences (LDS) instead of pseudo-random numbers. Methods based on the usage of such sequences are known as Quasi Monte Carlo (QMC) methods.

LDS are specifically designed to place sample points as uniformly as possible. Unlike random numbers, successive LDS points "know" about the position of previously sampled points and "fill" the gaps between them. LDS are also known as quasi random numbers. The QMC algorithm for the evaluation of the integral (14) has a form

$$I_N = \frac{1}{N}\sum_{i=1}^{N} f(q_i) \tag{15}$$

where q_i is a set of LDS points uniformly distributed in a unit hypercube H^n, $q_i = (q_i^1, ..., q_i^n)$.

There are a few well-known and commonly used LDS. Different principles were used for their construction by Holton, Faure, Sobol', Niederreiter and others. Many practical studies have proven that the Sobol' LDS is in many aspects superior to other LDS [10].

For the best known LDS the estimate for the rate of convergence $I_N \to I$ is known to be $O(ln^n N)/N$. This rate of convergence is much faster than that for the MC method, although it depends on the dimensionality n.

2.4.1 Numerical computation of the Sobol' indices

From (5), and applying the QMC algorithm for the evaluation of the integrals, the Sobol' indices can be calculated in a straightforward manner according to the formulas:

$$SI_{i,j} = \frac{\frac{1}{N}\sum y_j(p_i, \bar{p_i}) y_j(p_i, \bar{p_i}') - (\frac{1}{N}\sum y_j(p))^2}{\frac{1}{N}\sum y_j^2(p) - (\frac{1}{N}\sum y_j(p))^2} \tag{16}$$

$$SI_{i,j}^T = \frac{1}{2}\frac{\sum \left[y_j(p_i, \bar{p_i}) y_j(p_i', \bar{p_i})\right]^2}{\frac{1}{N}\sum y_j^2(p) - (\frac{1}{N}\sum y_j(p))^2} \tag{17}$$

Thus, each Quasi Monte Carlo sample point requires three computations of the model $y_j(p_i, \bar{p_i})$, $y_j(p_i', \bar{p_i})$ and $y_j(p_i, \bar{p_i}')$. For the computation of the Sobol' indices of an entire set of n parameters, using N sample points, the number of function evaluations is $N_F = N(n+2)$.

2.4.2 Numerical computation of the DGSM measures

Evaluation of DGSM measures requires calculation of $E_{i,j}(p^*)$. In [7] it is calculated analytically for easy-differentiable functions or numerically using finite difference approximation:

$$E_{i,j}(p^*) = \frac{\left[y_j(p_1^*, ..., p_{i-1}^*, p_i^* + \delta, p_{i+1}^*, ..., p_n^*) - y_j(p^*)\right]}{\delta} \tag{18}$$

where δ is a small increment.

Proper selection of scalar δ is crucial to maintaining acceptable round-off and truncation error levels. The total number of function evaluation for calculation of a full set of $\bar{G}_{i,j}^a$ is $N_F = N(n+1)$.

In order to reduce the number of function evaluations and to increase the precision of the sensitivity measures, the use of the direct decoupled method (DDM) to compute the partial derivatives of the ODEs systems is suggested. The sensitivity equations can be solved with ODESSA simultaneously with the original system avoiding the difficult task of selecting a proper δ and reducing the number of function evaluations to $N_F = N$.

2.5 Extension to ODEs systems

Since dealing with a systems of ODEs, the sensitivity indices of every observed state variable at each measurement time point with respect to each of the parameters, are available. In order to summarize all this information, global sensitivity indices are defined as the average of all the $SI_{i,j}$ for each parameter:

$$S_i = \frac{1}{N_y}\frac{1}{N_t}\sum_{j=1}^{N_y}\sum_{k=1}^{N_t} SI_{i,j}(t_k) \tag{19}$$

The same expression is applicable to $SI_{i,j}^T$, $\bar{M}_{i,j}$, $\bar{\Sigma}_{i,j}$ and $\bar{G}_{i,j}^a$.

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