



**HAL**  
open science

## An inference method for global sensitivity analysis

Gildas Mazo, Laurent Tournier

► **To cite this version:**

Gildas Mazo, Laurent Tournier. An inference method for global sensitivity analysis. *Technometrics*, 2024, <https://doi.org/10.1080/00401706.2024.2431113> . hal-04199638v3

**HAL Id: hal-04199638**

**<https://hal.inrae.fr/hal-04199638v3>**

Submitted on 5 Nov 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# An inference method for global sensitivity analysis

Gildas Mazo

Université Paris-Saclay, INRAE, MaIAGE, 78350, Jouy-en-Josas, France  
and

Laurent Tournier

Université Paris-Saclay, INRAE, MaIAGE, 78350, Jouy-en-Josas, France

October 30, 2024

## Abstract

Although there is a plethora of methods to estimate sensitivity indices associated with individual inputs, there is much less work on interaction effects of every order, especially when it comes to make inferences about the true underlying values of the indices. To fill this gap, a method that allows one to make such inferences simultaneously from a Monte Carlo sample is given. One advantage of this method is its simplicity: it leverages the fact that Shapley effects and Sobol indices are only linear transformations of total indices, so that standard asymptotic theory suffices to get confidence intervals and to carry out statistical tests. To perform the numerical computations efficiently, Möbius inversion formulas are used, and linked to the fast Möbius transform algorithm. The method is illustrated on two dynamical systems, both with an application in life sciences: a Boolean network modeling a cellular decision-making process involving 12 inputs, and a system of ordinary differential equations modeling some population dynamics involving 10 inputs.

*Keywords:* Sobol index, Möbius transform, higher order interaction effect, global sensitivity analysis, inference, computation

# 1 Introduction

The sensitivity analysis of mathematical models is important to gain insight into one's model, eventually suggesting potential avenues for model reduction, refinement, or guidance in the design of future experiments.

Sensitivity analysis seeks to quantify, for a given mathematical or computational model  $f$ , the extent to which a change in the inputs contributes to a change in the output. Contrary to local methods, which quantify rates of change around particular points in the input space, global sensitivity analysis assesses the inputs' contributions over the whole input space (Saltelli et al., 2008, 2000), often with statistical methods. One then adopts a probabilistic framework in which the inputs  $X = (X_1, \dots, X_d)$  are seen as random variables. From now on, by sensitivity analysis we shall mean global sensitivity analysis. We also assume throughout that the inputs  $X_1, \dots, X_d$  are mutually independent.

Different aspects of sensitivity analysis are captured by different kinds of sensitivity indices. The Sobol index  $\sigma^*(A)$ ,  $A \subset \{1, \dots, d\} =: D$ , quantifies the interaction effect of order  $|A|$  between the components of  $X_A$ , the subvector of  $X$  corresponding to the subset  $A$  (see, e.g. Saltelli et al. (2000)). In the special case where  $A = \{j\}$ ,  $j = 1, \dots, d$ , the quantity  $\sigma^*(\{j\}) = \text{Var E}(f(X)|X_j)$ , called the first-order Sobol index of  $X_j$ , is interpreted as the expected variance reduction of the output, should the input  $X_j$  be fixed (Iman and Hora, 1990; Janssen, 1994). The closed Sobol index  $\tau^*(A)$ , given by  $\text{Var E}(f(X)|X_A)$ , is a generalization of the first-order Sobol index to any subset  $A \subset D$ . We shall call it the dual index for a reason explained later. The total index  $\tau(A)$  is defined as the sum over all interaction effects  $\sigma^*(B)$ ,  $B \cap A \neq \emptyset$ , or, equivalently, as the output variability induced by a random change in  $X_A$ , averaged over the remaining inputs  $X_{D \setminus A}$ . Shapley effects stem from the application of an allocation method coming from cooperative game theory (Shapley, 1951; Winter, 2002). One assigns a “value” to each of the players, based

on the performance of all the possible coalitions among them. By analogy, one assigns a value—called the Shapley effect—to each of the inputs, based on all the possible input combinations. The Shapley effect  $\theta(\{j\})$  of the individual input  $X_j$  summarizes its global importance. The sum of the Shapley effects sums up to the output variance. (This is not true for the individual total indices or the individual Sobol indices.)

Estimation of sensitivity indices has attracted much attention in the literature. In particular, numerous methods have been proposed to estimate first-order Sobol indices. Many methods rest on the fact that  $\text{Var} E(f(X) - E[f(X)]|X_j)$  can be re-expressed as a simple expectation and use the method-of-moments to estimate it from a Monte Carlo or quasi-Monte Carlo sample of inputs (Sobol, 1993; Jansen, 1999; Janon et al., 2014; Gamboa et al., 2016; Homma and Saltelli, 1996; Saltelli, 2002; Saltelli et al., 2010; Owen, 2013). Asymptotic normality of some estimators is studied in Gamboa et al. (2016); Janon et al. (2014). To avoid the waste of data, more elaborate ways of combining outputs have been proposed (Tissot and Prieur, 2015; Gilquin et al., 2019; Saltelli et al., 2010; Saltelli, 2002), the goal being always to have the most efficient estimates with the least model runs (Piano et al., 2021). See also Saltelli et al. (1999) for another way of exploring the input space. Methods based on U-statistics are found in Gamboa et al. (2021). There are also methods that offer a different look, statistically speaking. For instance, nonparametric regression techniques, or techniques based on kernels, are found in Da Veiga et al. (2023); Da Veiga and Gamboa (2013); Solís (2019). The use of meta-models to compute sensitivity indices has been proposed as well (Sudret, 2008; Bénard et al., 2022). It is also possible to do the estimation from “given data”, that is, from a standard sample of inputs and outputs that was not primarily designed to perform a sensitivity analysis (Plischke et al., 2013). It is a fact that the estimation of first-order Sobol indices is an active area of research, and many other methods have been, and continue to be, proposed. For instance, the reader is referred to Prieur and Tarantola (2015) or Da Veiga et al. (2023) for more details and

possibly other estimation methods. A list of methods is also available in Iooss et al. (2020). A numerical comparison of some of the above methods is given in Kucherenko and Song (2017). Although a plethora of methods exist to estimate first-order indices, the literature is thinner about the estimation of higher-order interaction effects. Attention has increased recently, though, as they are useful to compute Shapley effects (Castro et al., 2009; Iooss and Prieur, 2019; Plischke et al., 2021; Song et al., 2016; Goda, 2021; Broto et al., 2020).

Rather than narrowing the estimation to particular sensitivity indices or effects, we can look at the problem of inference globally: the goal is then to extract, combine and assess the information provided by the four kinds of sensitivity indices and effects of all orders, thus paving the way for richer analyses. One advantage of such a global approach is that it takes into account the effects of interactions between inputs. These effects, indeed, carry important information when considering mathematical models of complex natural phenomena (Ball, 2023; Boyle et al., 2017). For instance, they explain a significant share of the total output variability in the two dynamical models (Calzone et al., 2010; De Paepe et al., 2016) analysed in Section 5 below. The first is a Boolean network modeling cell fate decision (Calzone et al., 2010) and the second is a differential system modeling microbial population dynamics (De Paepe et al., 2016). While these models were originally analysed with local and one-at-a-time approaches, we shall see that using a global approach and estimating higher order sensitivity indices gives the modeler valuable insight about the system's dynamical behavior, emphasizing possibly complex interactions between the system's parameters. These interactions may be relevant to the modeled system, or they can be mathematical artifacts of the model. In either case, estimating higher order indices will provide useful information when analyzing a complex mathematical model.

To address the problem of inference globally, an approach that exploits the linear mappings between the four kinds of sensitivity indices is proposed. The asymptotic normality of the estimator of the vector of total indices, the vector of dual indices, the vector of Sobol

indices and the vector of Shapley effects is established. The formulas of the asymptotic variance-covariance matrices of the estimators are given in closed form. Algorithms to compute the estimators and their asymptotic variance-covariance matrices are presented, analyzed, and discussed. To assess the statistical significance of the extracted information, several statistical tests are built.

The method is applied to two published dynamical systems, both with application in life sciences. The two systems are different in nature: the first one is a stochastic Boolean network modeling a cellular decision-making process introduced by Calzone et al. (2010); the second one is a deterministic differential system modeling population dynamics introduced by De Paepe et al. (2016). Both systems were analyzed with local approaches; here a global sensitivity analysis is proposed, including the estimation of total and Sobol indices as well as Shapley effects, and the analysis of those indices based on statistical testing. We show how such inferences can be used to gain insight on the systems' dynamics.

The rest of the paper is organized as follows. Section 2 is a brief review of the four major kinds of sensitivity indices. Section 3 presents the inference method, from the estimation of the sensitivity indices to asymptotic normality and hypothesis testing. The computational aspects are addressed in Section 4. Section 5 presents the sensitivity analysis of the two dynamical systems. Section 6 summarizes the results and discusses limitations and possible future developments.

## 2 Global sensitivity indices

The definition of the four major kinds of sensitivity indices—namely, Sobol, total, dual indices and Shapley effects—are recalled in this section. Let  $f(X)$  be the output of some real function  $f$  with real random inputs  $X := (X_1, \dots, X_d)$ . Recall that inputs are assumed to be mutually independent. Denote  $D = \{1, \dots, d\}$ . Let  $\mathbf{2}^D$  be the power set of  $D$ , that

is, the set of the subsets of  $D$ . For  $A \in \mathbf{2}^D \setminus \emptyset$ , the symbol  $X_A$  denotes the subvector of  $X = X_D = (X_1, \dots, X_d)$  that corresponds to  $A$ . For instance if  $d = 4$  and  $A = \{3, 1, 4\}$  then  $X_A = (X_1, X_3, X_4)$ .

If the components of  $X$  are mutually independent and  $\mathbb{E} f(X)^2 < \infty$  then it holds that  $f(X) = \sum_{A \subset D} f_A(X_A)$ , where the functions  $f_A$  satisfy

$$\mathbb{E}(f_A(X_A)|X_B) = 0 \text{ if } A \not\subset B. \quad (1)$$

Throughout, the subset symbol  $\subset$  is to be understood in the non-strict sense, meaning that  $A \subset A$  always holds. By convention,  $f(X_\emptyset; \emptyset)$  is a constant. Equation (1) characterizes the decomposition of  $f(X)$ : if there are functions  $f'_A$  that satisfy (1) and  $f(X) = \sum_{A \subset D} f'_A(X_A)$  then each  $f'_A(X_A)$  must be equal to  $f_A(X_A)$  almost surely. The above decomposition is called the Sobol decomposition, or Sobol-Hoeffding decomposition. For more details see Hoeffding (1948); Sobol (1993); van der Vaart (1998). This decomposition is the starting point to define the sensitivity indices.

**Sobol indices.** The Sobol-Hoeffding decomposition entails a decomposition of the variance of  $f(X)$ . Indeed, equation (1) implies that the random variables  $f_A(X_A)$  are uncorrelated, and hence  $\text{Var } f(X) = \sum_{A \subset D} \text{Var } f_A(X_A)$ . The quantities  $\sigma^*(A) := \text{Var } f_A(X_A)$  are called the Sobol indices (Prieur and Tarantola, 2015; Sobol, 1993). Sometimes Sobol indices refer to the normalized quantities  $\sigma^*(A)/\text{Var } f(X)$ ; in the present manuscript they mean the raw quantities. Note that  $\sigma^*(\emptyset) = 0$ . The Sobol indices associated with the singletons are called first order Sobol indices, or main effects, and the remaining indices are called interaction indices, or interaction effects. First order indices have an easy interpretation. Indeed, it is easy to see that

$$\sum_{B \subset A} f_B(X_B) = \mathbb{E}(f(X)|X_A) \quad (2)$$

and hence, taking  $A = \{j\}$ , one gets  $\sigma^*(\{j\}) = \text{Var } \mathbb{E}(f(X)|X_j) = \text{Var } f(X) -$

$E \text{Var}(f(X)|X_j)$ , which is the expected reduction in variance induced by fixing  $X_j$  to a random value.

**Example 1.** Let  $f(X) = f(X_1, X_2, X_3) = \sin X_1 + a \sin^2 X_2 + bX_3^4 \sin X_1$ , where  $X_1, X_2, X_3$  are independent random variables uniformly distributed on the interval  $(-\pi, \pi)$ . The Sobol indices are given by  $\sigma^*({1}) = 1/2 + b\pi^4/5 + b^2\pi^8/50$ ,  $\sigma^*({2}) = a^2/8$ ,  $\sigma^*({1, 3}) = (1/18 - 1/50)b^2\pi^8$ ,  $\sigma^*({3}) = \sigma^*({1, 2}) = \sigma^*({2, 3}) = \sigma^*({1, 2, 3}) = \sigma^*({\emptyset}) = 0$ , see e.g. Sobol and Levitan (1999).

We shall denote by  $\sigma^*$  the vector with components  $\sigma^*(A)$  and call it the Sobol index vector. The arrangement of the components in this vector is chosen arbitrarily. A specific arrangement will be chosen later on (Section 4) to facilitate computations.

**Dual indices (closed Sobol indices).** Taking the variance in both sides of (2), one gets that

$$\sum_{B \subset A} \sigma^*(B) = \text{Var } E(f(X)|X_A) =: \tau^*(A). \quad (3)$$

The index  $\tau^*(A)$  is sometimes called the closed Sobol index (Saltelli, 2002; Jansen, 1999) or subset importance (Liu and Owen, 2006) of  $A$ . We shall call it the dual total index of  $A$ , or simply the dual index of  $A$ . The reason stems from the duality relationship between  $\tau^*(A)$  and the total index  $\tau(A)$  defined in the next section, see equation (5) below. (See also Herin et al. (2024).) The dual index of  $A$  is the expected reduction in variance induced by fixing the components of  $X_A$ .

**Example 2** (Continuation of Example 1). *The dual index of  $\{1, 2\}$  is given by  $\tau^*({1, 2}) = \sigma^*({1}) + \sigma^*({2}) + \sigma^*({1, 2}) = \frac{1}{2} + \frac{b\pi^4}{5} + \frac{b^2\pi^8}{50} + \frac{a^2}{8}$ . The calculations for the remaining components are given in Section A of the supplementary file.*

The vector of dual indices will be denoted by  $\tau^*$ .



**Total indices.** The total index  $\tau(A)$  of  $A$  is defined as

$$\tau(A) = \sum_{B \cap A \neq \emptyset} \sigma^*(B). \quad (4)$$

Total indices were introduced in Homma and Saltelli (1996) for singletons. The quantity  $\tau(A)$  measures the sum of all interactions of  $X_A$  (Prieur and Tarantola, 2015). Note that  $\tau(D) = \text{Var } f(X)$  and  $\tau(\emptyset) = 0$ . By (4), it holds

$$\tau(D) - \tau(A) = \sum_{B \subset D} \sigma^*(B) - \sum_{B \cap A \neq \emptyset} \sigma^*(B) = \tau^*(D \setminus A), \quad (5)$$

where the last equality holds because of (3). It follows (Prieur and Tarantola, 2015)

$$\tau(A) = \text{E Var}(f(X)|X_{D \setminus A}). \quad (6)$$

Therefore, the total index of  $A$  is also interpreted as the output variance induced by a random change in  $X_A$ , averaged over all the remaining inputs. It is easy to see that  $\tau(A) = 0$  if and only if the function  $f$  does not depend on  $X_A$ . Thus, total indices are used in a “factor fixing” setting (Saltelli et al., 2008; Sobol, 1993).

**Example 3** (Continuation of Example 1). *The total index of  $\{1, 2\}$  is given by  $\tau(\{1, 2\}) = \sigma^*(\{1\}) + \sigma^*(\{2\}) + \sigma^*(\{1, 2\}) + \sigma^*(\{1, 3\}) + \sigma^*(\{2, 3\}) + \sigma^*(\{1, 2, 3\}) = \frac{1}{2} + \frac{b\pi^4}{5} + \frac{b^2\pi^8}{18} + \frac{a^2}{8}$ . The calculations for the remaining components are given in Section A of the supplementary file.*

The vector of total indices will be denoted by  $\tau$ .

**Shapley effects.** Shapley effects assess the global importance of each individual input (Owen, 2014). They result from an allocation method of cooperative game theory in which each player is assigned a value based on the effects of adding or removing that player in each possible coalition. If  $D$  is seen as a set of players, then to each coalition  $B \subset D$  there corresponds a real number, denoted by  $\text{val}(B)$ , which represents the “value” of

$B$ . It is assumed that  $\text{val}(\emptyset) = 0$ . The Shapley value of player  $j$ ,  $j = 1, \dots, d$ , is given by (Harsanyi, 1963)

$$\theta_{\text{val}}(\{j\}) = \sum_{B \cap \{j\} \neq \emptyset} \frac{\sum_{A \subset B} (-1)^{|B \setminus A|} \text{val}(A)}{|B|}. \quad (7)$$

The Shapley values satisfy  $\text{val}(D) = \sum_{j=1}^d \theta_{\text{val}}(\{j\})$ . See (Shapley, 1951; Winter, 2002) and Section B of the supplementary file for more details. If  $\text{val}$  is replaced by its dual  $\text{val}^*(B) = \text{val}(D) - \text{val}(D \setminus B)$  then  $\theta_{\text{val}}(\{j\}) = \theta_{\text{val}^*}(\{j\})$  for all  $j = 1, \dots, d$ . We say that the Shapley value is self-dual, see Funaki (1998); Oishi et al. (2016).

By an analogy between cooperative game theory and global sensitivity analysis (the individual inputs  $X_j$  play the role of the players), we can choose  $\text{val}(B)$  to be

$$\text{Var E}(f(X)|X_B) = \tau^*(B) \text{ or } \text{E Var}(f(X)|X_{D \setminus B}) = \tau(B),$$

as in Owen (2014) and Song et al. (2016), respectively. Both choices lead to the same sets of indices

$$\theta(\{j\}) := \theta_{\tau}(\{j\}) = \theta_{\tau^*}(\{j\})$$

by duality between  $\tau$  and  $\tau^*$ . The quantities  $\theta(\{j\})$  are called Shapley effects in sensitivity analysis and can be expressed in terms of Sobol indices as

$$\theta(\{j\}) = \sum_{B \cap \{j\} \neq \emptyset} \frac{\sigma^*(B)}{|B|}; \quad (8)$$

see Owen (2014). This formula is a consequence of (7) and the Möbius inversion formula discussed in Section 3 below.

**Example 4** (Continuation of Example 1). *The Shapley effect of  $\{3\}$  is given by  $\theta(\{3\}) = \sigma^*(\{3\}) + \frac{1}{2}\sigma^*(\{1, 3\}) + \frac{1}{2}\sigma^*(\{2, 3\}) + \frac{1}{3}\sigma^*(\{1, 2, 3\}) = \frac{4b^2\pi^8}{225}$ . The calculations for the remaining components are given in Section A of the supplementary file.*

Shapley effects in sensitivity analysis are interesting because they allow one to assess the global importance of the individual inputs by taking interactions into account in a

“fair” way. Indeed, as seen in (8), the interaction effects captured by the Sobol indices are divided by the size of the interaction. This leads to a fair allocation of the output variance: we have that  $\text{Var} f(X) = \sum_{j=1}^d \theta(\{j\})$ . Another advantage of Shapley effects is that they can be used when the inputs are not mutually independent (Owen and Prieur, 2017). We shall denote by  $\theta$  the vector of Shapley effects.

### 3 A global inference method

In global sensitivity analysis, Sobol indices are defined first and, then, total indices are defined as cumulative effects of Sobol indices. It is more convenient, however, to go the other way around: in the following total indices are first estimated as global effects of combinations of inputs and Sobol index estimates ensue through a linear transformation of the vector of total index estimates. Estimation and inference is then made straightforward even for higher-order Sobol indices. In summary, we consider the following steps:

1. Compute the vector of total indices.
2. Compute the vector of dual indices as a linear transformation of the vector of total indices.
3. Compute the vector of Sobol indices as a linear transformation of the vector of dual indices.
4. If needed, compute the vector of Shapley effects as a linear transformation of the vector of Sobol indices.

**Remark 1.** *The mention “if needed” above is to emphasize that the proposed inference method should not have as its primary goal the estimation of Shapley indices. For if that were the objective then there are methods that may be more appropriate as they bypass*

*the estimation of Sobol indices altogether (Goda, 2021). Here, the estimation of Shapley indices should be seen as a by-product: once the Sobol indices are calculated, the estimation of Shapley effects is almost free.*

By inference it is meant the ability to take into account the Monte Carlo error in the insights, statements and conclusions drawn from the data. This shall take the form of confidence intervals and p-values associated with statistical tests of hypotheses.

The steps above are described in more detail below. Section 3.1 presents the estimators and Section 3.2 presents results and methods to make inferences.

### 3.1 Estimation of the sets of indices

The estimation of the four kinds of sensitivity index vectors by following the four steps above is addressed next.

**Total indices.** Let  $X' = (X'_1, \dots, X'_d)$  be an independent copy of  $X$ . If  $A \in \mathbf{2}^D$ , denote by  $X^{\setminus A}$  the vector made out of  $X$  and  $X'$  such that the components of  $X$  indexed by the members of  $A$  are replaced by those of  $X'$ . For instance, if  $d = 4$  and  $A = \{3, 1, 4\}$  then  $X^{\setminus A} = (X'_1, X_2, X'_3, X'_4)$ ,  $X^{\setminus \emptyset} = X$  and  $X^{\setminus D} = X'$ . Since we assumed mutually independent inputs, the total index associated with  $A$  given in (6) can be rewritten as

$$\tau(A) = \mathbb{E} \frac{1}{2} (f(X) - f(X^{\setminus A}))^2. \quad (9)$$

The above formula, known as Jansen's formula (Jansen, 1999), has the advantage that total indices are expressed as simple expectations, and hence simple moment estimators are available. It suffices to draw a sample from  $(X, X')$ , say of size  $n$ , and substitute the empirical average for the expectation in (9). More precisely, for each  $i = 1, \dots, n$ , draw two independent copies  $X^{(i)} = (X_1^{(i)}, \dots, X_d^{(i)})$  and  $X'^{(i)} =$

$(X_1^{(i)}, \dots, X_d^{(i)})$  and then perform the steps below:

$$\left\{ \begin{array}{l} \text{for each } A \in \mathbf{2}^D \\ \text{make } X^{(i)\setminus A} \text{ out of } X^{(i)} \text{ and } X'^{(i)} \\ \text{compute } f(X^{(i)\setminus A}). \end{array} \right. \quad (10)$$

One then obtains an estimator

$$\hat{\tau}(A) = \frac{1}{n} \sum_{i=1}^n \frac{1}{2} (f(X^{(i)}) - f(X^{(i)\setminus A}))^2 \quad (11)$$

for each  $A \subset D$ . Denote by  $\hat{\tau}$  the estimator of the vector  $\tau$  obtained as above.

**Dual indices.** Estimation of the dual index vector  $\tau^*$  can be done from (5). Note that there is a matrix  $L$  such that  $\tau^* = L\tau$ . More precisely, if  $L(A, B)$  denotes the element of  $L$  at the row and column corresponding to the nonempty sets  $A$  and  $B$ , respectively, then

$$L(A, B) = \begin{cases} -1 & \text{if } B = D \setminus A \\ 1 & \text{if } B = D \\ 0 & \text{otherwise.} \end{cases}$$

(By convention we may choose  $L(\emptyset, \emptyset) = 1$  and  $L(\emptyset, B) = 0$  for all  $B \neq \emptyset$ . For instance, if  $d = 2$  then

$$\begin{pmatrix} 0 \\ \tau^*({2}) \\ \tau^*({1}) \\ \tau^*({1, 2}) \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & -1 & 1 \\ 0 & -1 & 0 & 1 \\ 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} 0 \\ \tau({2}) \\ \tau({1}) \\ \tau({1, 2}) \end{pmatrix}.$$

Note that the expression of matrix  $L$  depends on the chosen order of the components of  $\tau$ . We shall denote by  $\hat{\tau}^*$  the estimator of the vector  $\tau^*$ .

**Sobol indices.** A decomposition of the output variance  $\text{Var } f(X)$  is easily obtained from the vector of dual indices  $\tau^*$ , see Liu and Owen (2006). Let  $\tau^*$  and  $\sigma^*$  momentarily

denote *arbitrary* real maps defined on  $\mathbf{2}^D$ , with  $\tau^*(\emptyset) = \sigma^*(\emptyset) = 0$ . Then it holds that

$$\tau^*(A) = \sum_{B \subset A} \sigma^*(B) \quad (\text{for every } A \in \mathbf{2}^D) \quad (12)$$

and

$$\sigma^*(A) = \sum_{B \subset A} (-1)^{|A \setminus B|} \tau^*(B) \quad (\text{for every } A \in \mathbf{2}^D) \quad (13)$$

are equivalent. The pair of equations (12) and (13) is known as Möbius inversion formulas. The equivalence is a direct consequence of a result from Rota (1964) on finite partially ordered sets. Now, let us come back to sensitivity analysis and let the total index vector be defined through (9). Let  $\tau^*$  be the dual index vector of  $\tau$ . Both vectors can be estimated directly as seen above. Then let  $\sigma^*$  be defined through (13). Since  $\tau^*(D) = \text{Var } f(X)$ , taking  $A = D$  in (12) *de facto* provides a decomposition of the output variance  $\text{Var } f(X)$ . It is not difficult to show that, in fact, the quantities  $\sigma^*(A)$  coincide with the Sobol indices as defined in Section 2. The maps  $\tau^*$  and  $\sigma^*$  are sometimes known as Möbius transforms of one another (Björklund et al., 2007; Grabisch et al., 2000; Kennes, 1992).

**Remark 2.** *Since Möbius inversion formulas hold for arbitrary maps, we can define a vector  $\sigma$  from the vector  $\tau$  the same way  $\sigma^*$  was defined from  $\tau^*$ . Since  $\tau(D)$  is also equal to  $\text{Var } f(X)$ , this defines another variance decomposition. By the same reasoning, every real map  $\tau$  defined on  $\mathbf{2}^D$  with  $\tau(\emptyset) = 0$  and  $\tau(D) = \text{Var } f(X)$  leads to a variance decomposition. According to Il Idrissi et al. (2023), the choice (13) is justified because of the Sobol-Hoeffding decomposition for mutually independent inputs.*

From (13), it is then clear that

$$\sigma^* = M^* \tau^*, \quad (14)$$

where  $M^*$  is the matrix with entries

$$M^*(A, B) = \begin{cases} (-1)^{|A \setminus B|} & \text{if } B \subset A, \\ 0 & \text{otherwise.} \end{cases}$$

(As noted in Grabisch et al. (2000); Plischke et al. (2021), the absolute value of  $M^{*\top}$  is equal to the Sierpinski matrix, a fractal matrix.) We shall denote by  $\hat{\sigma}^*$  the estimator of the vector  $\sigma^*$  obtained by substituting  $\hat{\tau}^*$  for  $\tau^*$  in (14).

**Shapley effects.** In view of (8), there is a matrix  $N^*$  of size  $d \times 2^d$  such that

$$\theta = N^* \sigma^*. \tag{15}$$

From (8), it is easily seen that if  $\{k\}$  and  $B$  are the  $i$ th and  $j$ th elements in some arbitrary list of the subsets of  $D$ , then the entry at the  $i$ th row and  $j$ th column of  $N^*$  is given by

$$N^*(\{k\}, B) = \begin{cases} 1/|B| & \text{if } \{k\} \cap B \neq \emptyset, \\ 0 & \text{otherwise.} \end{cases}$$

We shall denote by  $\hat{\theta}$  the estimator of the vector  $\theta$  obtained by substituting  $\hat{\sigma}^*$  for  $\sigma^*$  in (15).

## 3.2 Making the inferences

The asymptotic normality of the estimators is established and utilized to calculate asymptotic confidence intervals, p-values, and test various hypotheses. A reminder about asymptotic confidence intervals and hypothesis testing is given in Section C of the supplementary file. For numerical examples and illustrations, see Section 5.

### Asymptotic normality and confidence intervals

It is established below that the sensitivity index estimators converge to multivariate normal distributions as the sample size grows. Based on this result, various tests are then built.

**Proposition 1.** *It holds that*

(i)  $\sqrt{n}(\hat{\tau} - \tau) \xrightarrow{d} N(0, T)$ , where  $T$  is the variance-covariance matrix with elements

$$T(A, B) = \text{Cov}((f(X) - f(X \setminus A))^2/2, (f(X) - f(X \setminus B))^2/2), \quad A, B \subset D;$$

(ii)  $\sqrt{n}(\hat{\tau}^* - \tau^*) \xrightarrow{d} N(0, T^*)$ , where  $T^* = LTL^\top$ ;

(iii)  $\sqrt{n}(\hat{\sigma}^* - \sigma^*) \xrightarrow{d} N(0, \Sigma^*)$ , where  $\Sigma^* = M^*T^*M^{*\top}$ .

(iv)  $\sqrt{n}(\hat{\theta} - \theta) \xrightarrow{d} N(0, \Theta)$ , where  $\Theta = N^*\Sigma^*N^{*\top}$ .

The proof of Proposition 1 follows from a direct application of the central limit theorem and the linear relationships between the estimators; see e.g. van der Vaart (1998).

**Remark 3.** *While the estimator  $\hat{\tau}$  is conceptually simple, there exist more efficient asymptotically normal estimators. Two examples are offered in Section D of the supplementary file. One of them generalizes an estimator considered Azzini et al. (2021).*

The matrix  $T$  can be estimated by computing empirical covariances. Let us denote by  $\hat{T}$  the estimate of  $T$ . From  $\hat{T}$ , estimates  $\hat{T}^*$ ,  $\hat{\Sigma}^*$  and  $\hat{\Theta}$  of  $T^*$ ,  $\Sigma^*$  and  $\Theta$ , respectively, can be constructed by applying the formulas in Proposition 1. To avoid possible complications due to the fact that the entries of  $T$  corresponding to the empty set will be null, we may remove from  $\hat{\tau}$  and  $\tau$  the component corresponding to the empty set. Proposition 1 allows us to build asymptotic confidence intervals as explained in Section C of the supplementary file.

## Hypothesis testing

Let us introduce some notation. If  $\beta \in (0, 1)$ , let  $q_\beta$  denote the quantile of order  $\beta$  of a standard normal distribution. Let  $\Phi$  denote the cumulative distribution function of a standard normal distribution. Remember that to decide between a null hypothesis  $H_0$  and an alternative  $H_1$ , one computes a statistic  $S_n$  from the data and rejects  $H_0$  if  $S_n$  belongs



to some “rejection set” assumed to be of the form  $(r, \infty)$ . The so-called type I and type II errors of the test are given by  $\Pr_{H_0}(S_n > r)$  (probability of rejecting  $H_0$  while it is true) and  $\Pr_{H_1}(S_n \leq r)$  (probability of accepting  $H_0$  while  $H_1$  is true), respectively. The p-value of the test is given by  $\Pr_{H_0}(S_n > s_n^{(\text{obs})})$  (probability under  $H_0$  of observing a statistic beyond the one actually observed in the data), where  $s_n^{(\text{obs})}$  stands for the statistic actually observed in the dataset at hand. Given some level of significance  $1 - \alpha \in (0, 1)$ , one seeks the least critical value  $r$  such that  $\Pr_{H_0}(S_n > r) \leq \alpha$ . If it is known that  $S_n$  obeys a standard normal distribution then  $r = q_{1-\alpha}$  and the test can be carried out. Otherwise one wants to establish that  $S_n$  is approximately normal and get approximate critical values.

Based on the asymptotic normality established in Proposition 1, various tests are built below.

**Nullity of a given sensitivity index.** Let  $\psi$  denote any of  $\tau, \tau^*, \sigma^*, \theta$  and let  $\hat{\psi}$  denote its estimate. Let  $\Psi$  denote the asymptotic variance-covariance matrix of  $\hat{\psi}$ , that is,  $\sqrt{n}(\hat{\psi} - \psi) \xrightarrow{d} N(0, \Psi)$ . Let  $\hat{\Psi}$  denote a consistent estimate of  $\Psi$ . A formal test is given by

$$H_0 : \psi(A) = 0 \text{ versus } H_1 : \psi(A) \neq 0. \quad (16)$$

To carry out this test, we can take the statistic  $S_n = \sqrt{n}\hat{\psi}(A)/\sqrt{\hat{\Psi}(A, A)}$  and the critical value  $r = q_{1-\alpha/2}$ . The p-value is given by  $1 - \Phi(S_n)$ . Note: it may have been noticed that if  $\tau(A) = 0$  then the estimator is also zero. But the purpose of the test above is not so much to know whether a quantity is exactly zero as to know whether it can be assumed to be zero in regard to the data at hand.

**Presence of interactions between a given input and the other ones.** It is well known that  $\tau^*({j}) \leq \tau({j})$  and that  $\tau({j}) - \tau^*({j})$  quantifies the strength of interactions involving input  ${j}$ . A formal test is given by

$$H_0 : \tau^*({j}) = \tau({j}) \text{ versus } H_1 : \tau^*({j}) < \tau({j}). \quad (17)$$

To carry out this test, we can take the statistic  $S_n = \sqrt{n}a_j^\top \widehat{\tau} / \sqrt{a_j^\top \widehat{T} a_j}$ , where  $a_j$  is the vector of length  $2^d$  comprising only zeros, except at the positions corresponding to  $\{j\}$ ,  $D \setminus \{j\}$  and  $D$  where the components are equal to 1, 1 and  $-1$ , respectively. The critical value is given by  $r = q_{1-\alpha}$ . The p-value is given by  $1 - \Phi(S_n)$ .

**Contribution of a given set of Sobol indices to the total variance.** Suppose we want to test whether a given set of Sobol indices contributes to less than a certain share of the total variance. The above test can be formulated as

$$\begin{aligned} H_0 : \sum_{i=1}^k \sigma^*(A_i) &\leq (1 - \eta) \text{Var } f(X), \text{ versus} \\ H_1 : \sum_{i=1}^k \sigma^*(A_i) &> (1 - \eta) \text{Var } f(X), \end{aligned} \quad (18)$$

where  $\eta \in (0, 1)$  is some desired threshold and  $\sigma^*(A_1), \dots, \sigma^*(A_k)$  are chosen Sobol indices. Here  $A_1, \dots, A_k$  can be any subsets of  $D$  (except the empty set). To carry out this test, proceed as follows. Let  $j_i$  denote the position of  $\sigma^*(A_i)$  in the vector  $\sigma^*$ . Define the vector  $c = (c_1, \dots, c_{2^d-1})$ , where  $c_{j_i} = \eta/(1 - \eta)$  for  $i = 1, \dots, k$ , and  $-1$  otherwise. Take the test statistic and the critical value

$$S_n = \frac{\sqrt{nc^\top \widehat{\sigma}^*}}{\sqrt{c^\top \widehat{\Sigma}^* c}}, \quad r = q_{1-\alpha}, \quad (19)$$

respectively. Note that the test depends on  $\eta$ . The higher the contribution level  $1 - \eta$ , the less we will tend to reject  $H_0$ . Indeed, conditionally on the data,  $S_n = S_n(\eta)$  is an increasing function of  $\eta$  on  $[0, 1]$ .

**Proposition 2.** *With the given  $S_n$  and  $r$ , it holds that:*

- (i) *The tests (16) and (17) satisfy  $\lim_{n \rightarrow \infty} \Pr_{H_0}(S_n > r) = \alpha$ .*
- (ii) *The test (18) satisfies  $\lim_{n \rightarrow \infty} \Pr_{H_0}(S_n > r) \leq \alpha$ .*

The first statement of Proposition 2 is a direct application of standard theory. The second statement is proved in Section G of the supplementary file.

Examples of applications of the above tests are given in Section 5.

## 4 Computational aspects

Estimators and their asymptotic variance-covariance matrices have been defined in Section 3. However, it may not be immediately apparent from the given formulas how to actually perform the computations, and at what expense. In this section, we assume that the sample of model outputs has already been generated. Thus, in the following *computation expense* is understood as the expense of the inference method *per se*, and not the expense of the sensitivity analysis as a whole. A discussion about the computation expense of the sensitivity analysis as a whole is given in Section 6.

In what follows, computation expense will be synonymous with number of arithmetic operations. Also, we shall use the “Big Theta” notation (Knuth, 1997) : two functions  $f$  and  $g$  of  $d$  satisfy  $g(d) = \Theta(f(d))$  if  $|g(d)/f(d)|$  remains bounded from above and away from zero, as  $d$  goes to infinity. For instance, the computation expense of  $\hat{\tau}$  is  $\Theta(n2^d)$ , meaning that it is proportional to  $n2^d$  as  $d \rightarrow \infty$ . Finally, if  $M$  is a matrix, let  $\text{nnz}(M)$  denote the number of nonzero elements of  $M$ .

The computations and their implementation is greatly facilitated once the elements of the power set have been arranged in some specific order: associate with each  $A \in \mathbf{2}^D$  a Boolean vector of size  $d$  and order the Boolean vectors according to the lexicographical order, most significant bit first. An example is given in Table 1.

With the above arrangement, “building” the matrix  $M^*$  in (14) becomes straightforward, as shows Proposition 3.

**Proposition 3.** *If the components of  $\tau^*$  and  $\sigma^*$  are arranged as described above then the*

|             |         |         |           |         |           |           |             |
|-------------|---------|---------|-----------|---------|-----------|-----------|-------------|
| (0,0,0)     | (0,0,1) | (0,1,0) | (0,1,1)   | (1,0,0) | (1,0,1)   | (1,1,0)   | (1,1,1)     |
| $\emptyset$ | $\{3\}$ | $\{2\}$ | $\{2,3\}$ | $\{1\}$ | $\{1,3\}$ | $\{1,2\}$ | $\{1,2,3\}$ |

Table 1: Arrangement of the subsets of  $D = \{1, \dots, d\}$  according to the lexicographical order in the Boolean space  $\{0, 1\}^d$  for  $d = 3$ .

matrix  $M^*$  in (14) is a  $d$ -fold Kronecker autoproduct of the  $2 \times 2$  matrix

$$M_1^* = \begin{pmatrix} 1 & 0 \\ -1 & 1 \end{pmatrix}. \quad (20)$$

In other words,

$$M^* = \otimes^d M_1^* = M_1^* \otimes \dots \otimes M_1^*, \quad (21)$$

where  $\otimes$  denotes the Kronecker product.

A proof of (21) is given in Section G of the supplementary file. See also Grabisch et al. (2000). To compute  $\sigma^* = M^* \tau^*$  from  $\tau^*$ , one can simply perform the product between the sparse matrix  $M^*$  and the vector  $\tau^*$ . Indeed, the matrix  $M^*$  is sparse since  $\text{nnz}(M^*) = \text{nnz}(\otimes^d M_1^*) = \text{nnz}(M_1^*)^d = 3^d$ ; see also, e.g. La Haye (2009). The expense of computing  $\sigma^*$  from  $\tau^*$  is then  $\Theta(\text{nnz}(M^*)) = \Theta(3^d)$ . Similarly, the matrix  $\Sigma^* = M^* T^* M^{*\top}$  defined in Proposition 1 can be computed by multiplying  $T^*$  to the left by  $M^*$  and then multiplying the result to the right by  $M^{*\top}$ . By the same token, the expense for computing  $\Sigma^*$  from  $T^*$  is  $\Theta(6^d)$ .

It turns out that there are—at least in principle—less expensive algorithms to compute  $\sigma^*$  from  $\tau^*$  and  $\Sigma^*$  from  $T^*$ . These algorithms are presented below.

## 4.1 The fast Möbius transform

The so-called fast Möbius transform can be used to compute  $\sigma^*$  from  $\tau^*$ . Suppose momentarily that  $\tau^*$  is an arbitrary vector of size  $2^d$  and  $M_1^*$  is an arbitrary matrix of size  $2 \times 2$ .

Let  $\sigma^{*(0)}, \sigma^{*(1)}, \dots, \sigma^{*(d)}$  be defined through the recurrence relations

$$\begin{cases} \sigma^{*(0)} &= \tau^* \\ \sigma^{*(j)} &= (I_{2^{d-j}} \otimes M_1^* \otimes I_{2^{j-1}}) \sigma^{*(j-1)}, \quad j = 1 \dots d, \end{cases} \quad (22)$$

where  $I_{2^{d-j}}$  and  $I_{2^{j-1}}$  denote the identity matrices of size  $2^{d-j}$  and  $2^{j-1}$ , respectively. (In general, if  $k$  is an integer then  $I_k$  will denote the identity matrix of size  $k$ .) The recurrence relations (22) define an algorithm in which the vector  $\sigma^{*(j)}$  is first initialized to the vector  $\tau^*$  and then updated at each iteration  $j = 1, \dots, d$ .

**Proposition 4.** *If  $\tau^*$  is a vector of size  $2^d$  and  $M_1^*$  is a nonnull matrix of size  $2 \times 2$  then the last update of (22) is equal to*

$$\sigma^{*(d)} = (\otimes^d M_1^*) \tau^*. \quad (23)$$

*Moreover, the total number of arithmetic operations needed to reach  $\sigma^{*(d)}$  is  $\Theta(d2^d)$ .*

A proof of Proposition 4 is given in Section G of the supplementary file. See also Björklund et al. (2007); Dayar and Orhan (2015); Fernandes et al. (1998); Grabisch et al. (2000); Kennes (1992); Yates (1937).

It follows from Proposition 4 that the computation of  $(\otimes^d M_1^*) \tau^*$  is less expensive with (22) than with standard sparse matrix multiplication as soon as  $\text{nnz}(M_1^*) > 2$ , because  $\text{nnz}(\otimes^d M_1^*) = \text{nnz}(M_1^*)^d$ . In terms of computer memory usage, algorithm (22) is preferable because it does not need to store the whole matrix  $\otimes^d M_1^*$ .

Remember that in Proposition 4 the vector  $\tau^*$  and the matrix  $M_1^*$  were arbitrary. Now take  $\tau^*$  to be the actual dual index vector with components arranged as in Table 1 and  $M_1^*$  the matrix (20). Then, in view of (14) and Proposition 4, the vector  $\sigma^{*(d)}$  is the Sobol index vector with components arranged as in Table 1. Note that instead of using matricial operations, the recurrence relations (22) can be implemented more efficiently by using “bit-shift” manipulations; see Section E.1 of the supplementary file. A numerical experiment

with reported computational gains is given in Section E.2. A Matlab implementation is available as part of the Supplementary Material.

**Remark 4.** *Algorithm (22) with  $M_1^*$  the absolute value of (20) is referred to as the fast Möbius transform in Björklund et al. (2007); Kennes (1992). Indeed, if  $\sigma^*$  is a real map defined on  $\mathbf{2}^D$  then the map defined by  $\tau^* : \mathbf{2}^D \rightarrow \mathbf{R}$ ,  $\tau^*(A) = \sum_{B \subset A} \sigma^*(B)$  is the Möbius transform of  $\sigma^*$ , see Björklund et al. (2007); Kennes (1992). The fast Möbius transform is then a “fast” algorithm to compute the Möbius transform from its inverse (as the fast Fourier transform computes the Fourier transform rapidly, hence the name). Computing the inverse from the Möbius transform (that is, algorithm (22) with  $M_1^*$  as in (20)) is, in essence, the same algorithm. An early version was given in Yates (1937).*

## 4.2 The extended fast Möbius transform

Along with the sensitivity index estimates, we need to compute their asymptotic variance-covariance matrices, too. Algorithm (22) can be extended to compute  $\Sigma^*$  from  $T^*$  the same way  $\sigma^*$  was computed from  $\tau^*$ . As before suppose momentarily that  $T^*$  is an arbitrary matrix of size  $2^d \times 2^d$  and  $M_1^*$  is an arbitrary matrix of size  $2 \times 2$ . Let  $\Sigma^{*(0)}, \Sigma^{*(1)}, \dots, \Sigma^{*(d)}$  be defined through the recurrence relations

$$\begin{cases} \Sigma^{*(0)} &= T^* \\ \Sigma^{*(j)} &= (I_{2^{d-j}} \otimes M_1^* \otimes I_{2^{j-1}}) \Sigma^{*(j-1)} (I_{2^{d-j}} \otimes M_1^{*\top} \otimes I_{2^{j-1}}) \quad (j = 1, \dots, d), \end{cases} \quad (24)$$

The difference between (22) and (24) is that we now consider a matrix which is updated with both left and right multiplications. A proposition similar to Proposition 4 holds.

**Proposition 5.** *If  $T^*$  is an arbitrary matrix of size  $2^d \times 2^d$  and  $M_1^*$  is an arbitrary nonnull matrix of size  $2 \times 2$  then the last update of (24) is equal to*

$$\Sigma^{*(d)} = (\otimes^d M_1^*) T^* (\otimes^d M_1^{*\top}). \quad (25)$$

Moreover, the total number of arithmetic operations needed to reach  $\Sigma^{*(d)}$  is  $\Theta(d4^d)$ .

The proof of Proposition 5 is an easy adaptation of the proof of Proposition 4 and is not given. The expense  $\Theta(d4^d)$  is to be compared with  $\Theta(6^d)$  that was obtained with sparse matrix multiplication.

As in Section 4.1, it now suffices to take  $T^*$  to be the variance-covariance matrix defined in Proposition 1 with its rows and columns arranged as in Table 1 and  $M_1^*$  the matrix (20). We then get that  $\Sigma^{*(d)} = (\otimes^d M_1^*)T^*(\otimes^d M_1^{*\top}) = (\otimes^d M_1^*)T^*(\otimes^d M_1^*)^\top = M^*T^*M^{*\top}$  coincides with the matrix  $\Sigma^*$  of Proposition 1. As for (22), a direct implementation is possible but there is a “bit-shift”, more efficient, version; see Section E.1 of the supplementary file. A numerical experiment with reported computational gains is given in Section E.2. A Matlab implementation is available as part of the Supplementary Material.

## 5 Application to the sensitivity analysis of two dynamical systems

In this section we apply the inference method to analyze the sensitivity of two different dynamical systems, both with an application in life sciences. The first one is a discrete system, more precisely a stochastic Boolean model of a cellular regulatory network, and the second one is a system of deterministic ordinary differential equations (ODE) modeling some population dynamics. In both cases, after identifying  $d$  key parameters, a  $n \times 2^d$  dataset is simulated according to part 3.1. The different sets of sensitivity indices are then estimated and are used, both qualitatively and quantitatively, to gain insight on the systems’ dynamical behavior. All the following computations were performed with MATLAB (R2023b).

## 5.1 A Boolean network modeling cell fate decision

First we consider a Boolean network, originally proposed by Calzone et al. (2010), modeling the decision-making process of a eukaryote cell between different “death pathways”. When subject to specific membrane receptors such as  $\text{TNF}\alpha$  (Tumor Necrosis Factor), cells can trigger inner antagonistic signaling pathways ultimately leading to the programmed death of the cell or, on the contrary, to its survival. Two types of death are considered: apoptosis, which is the classical programmed cell death, and necroptosis, which is a programmed death sharing apoptotic regulators yet presenting necrotic features (thereafter, this phenotype will be abusively denoted by “necrosis”). The model of Calzone et al. (2010) is an asynchronous Boolean network modeling the main regulatory pathways responsible for the decision between three phenotypes: apoptosis, necrosis and survival. In such networks, signaling molecules are represented by Boolean variables denoting their absence or presence, and regulatory processes are modeled through logical functions. Variables update asynchronously, implying that a state may transition to several possible successors. When associating probabilities to such transitions, the transition graph of the network straightforwardly translates to an absorbing Markov chain. It then becomes possible to compute the probability to enter apoptosis, necrosis or survival, starting from any given initial condition. More details on asynchronous Boolean networks and their translation into Markov chains can be found for instance in Tournier and Chaves (2009).

A critical point in the interpretation of the model’s outputs lies in the choice of the transition probabilities and by default, all successors of a state are assumed equiprobable. In reality those probabilities are linked to the relative speeds of the regulatory processes involved. Defining them from biological experiments for such a complex network, with multiple and heterogeneous intertwined pathways, is out of reach. This makes a global sensitivity analysis particularly appealing, to help detect which regulatory mechanisms, or



combinations of regulatory mechanisms, have the most impact on the dynamics, and are therefore priority targets for further investigation. A first sensitivity analysis of the model was performed by Zinovyev et al. (2012). The idea was to affect a positive weight to each Boolean variable: a weight greater than 1 means that processes involving the variable are rapid and the transitions updating the variable are favored, while a weight lower than 1 means that the processes are slow and the transitions are hindered. Mathematically, this boils down to parameterize the transition matrix of the Markov chain. Since the network is asynchronous, each nonnull entry corresponds to a switch of a single variable, and now contains the (normalized) weight associated with that variable. A local sensitivity analysis around the reference vector  $(1, \dots, 1)$  was performed by using a “one-at-a-time” approach, each weight varying independently around its reference value 1.

Here, we refine this approach by considering two types of weights instead of one: one controls the variable’s activation (from 0 to 1) and one its deactivation (from 1 to 0). This comes from the basic observation that in cell biology, production and degradation of a given compound may have very different time scales. Also, we now perform a global sensitivity analysis, which is preferable because it does not give any particular importance to the reference vector  $(1, \dots, 1)$ . Six variables central to the decision process are chosen: C8 (caspase 8), RIP1, NFkB, cIAP, MOMP and MPT. This leads to  $d = 2 \times 6 = 12$  inputs, corresponding to the 12 weights that parameterize the transition matrix of the Markov chain. The reader is referred to Calzone et al. (2010) for a comprehensive description of these biological variables and the regulatory processes they are involved in.

A dataset of  $n2^d = 1000 \times 4096$  model simulations was generated according to (10). The inputs were drawn independently from log-uniform distributions. See Table 1 in the supplementary file for details. Each simulation consists in the computation of three outputs: the probabilities to reach the three expected phenotypes (apoptosis, necrosis and survival) starting from a given initial condition. The detailed procedure is described in Section F of

the supplementary file. For each output, total and Sobol indices as well as Shapley effects are then estimated as described in Section 3. The estimates and their asymptotic variance-covariance matrices are computed with the “bit-shift” versions of the fast Möbius transform and the extended fast Möbius transform algorithms, respectively, given in Section 4. The choice of the size  $n$  of the Monte Carlo sample was arbitrary, but the obtained confidence intervals are narrow enough (see Figure 1) to draw reliable inferences. (Remember that to halve the standard error, four times more simulations are needed.)

The estimates are depicted in Figure 1. The first observation that can be made is that the “necrosis” phenotype seems qualitatively different from the other two, with generally lower index values, indicating a globally low variability of this output. We confirmed this result by drawing histograms of the three outputs in Figure 3 of the supplementary file. By inspecting highest Sobol index estimates in “apoptosis” and “survival” phenotypes (Fig. 1, middle row), we find that the three most important inputs are C8+, RIP1+ and NFkB+, as was originally observed by Zinovyev et al. (2012). To go beyond this qualitative observation, we apply Test (18) above and find these three inputs contribute to more than 85% of the total variance in each case, with respective p-values  $2.5 \times 10^{-3}$  and  $9.8 \times 10^{-3}$ . Although the combination  $A = \{C8+, RIP1+\}$  stands out as the fourth highest Sobol index in both cases, statistical inference invalidates this result. Indeed, testing the nullity of  $\sigma(\{C8+, RIP1+\})^*$  (test (16) above) leads to high p-values:  $p > 0.12$  for apoptosis and  $p > 0.15$  for survival, indicating the uncertainty on the estimation is too high to be conclusive. The interpretation of the “necrosis” phenotype is slightly more delicate. If on a qualitative level input NFkB+ stands out as the sole significant one, it can only be shown to contribute to 45% of total variance with high confidence (p-value  $< 0.05$ ). To explain more than 85% of the variance with p-value  $< 0.05$ , one has to consider the seven highest main or interaction effects  $\sigma^*(\{NFkB+\})$ ,  $\sigma^*(\{C8+\})$ ,  $\sigma^*(\{MPT+\})$ ,  $\sigma^*(\{NFkB+, C8+\})$ ,  $\sigma^*(\{RIP1+\})$ ,  $\sigma^*(\{NFkB+, RIP1+\})$  and  $\sigma^*(\{RIP1+, MPT+\})$ . This indicates that, al-

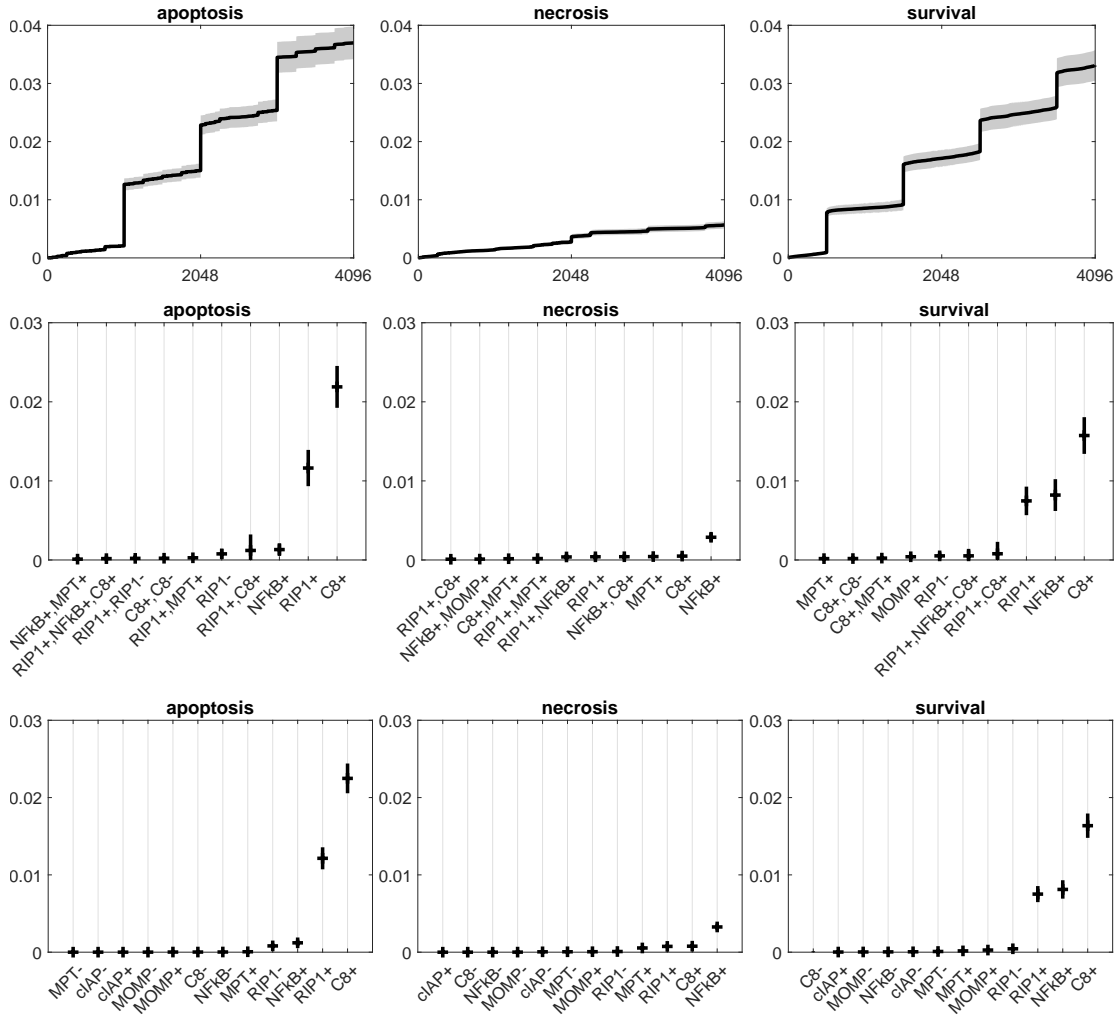


Figure 1: Global sensitivity analysis of the cell fate Boolean model by Calzone et al. (2010). The first row shows total index estimates for all  $2^d = 4096$  combinations of inputs, arranged in ascending order. The second row shows the 10 highest Sobol index estimates in ascending order; the third row shows Shapley effect estimates, also in ascending order. Each estimate is drawn within its 95% confidence interval. For reference, total output variances are respectively 0.0368 (apoptosis), 0.0056 (necrosis) and 0.0331 (survival), as indicated by the rightmost values in the top graphs.

though the variability of the phenotype is globally lower (Fig. 3), it is much more spread out than for the other two phenotypes. The choices between apoptosis and non-apoptosis, and between survival and non-survival are less complex, as they almost exclusively depend on a few key inputs, namely C8+ and RIP1+. Looking at the bottom row of Figure 1, very similar interpretations can be drawn from Shapley effect estimates, although the seemingly complex interactions between inputs for necrosis are globally missed.

Finally, it is interesting to note that total index estimates (Fig. 1, top row) are relatively well separated into small numbers of clusters, especially for apoptosis and survival. Furthermore, there seems to be a striking relationship between those plateaus and highest Sobol indices. For instance, the highest plateau of apoptosis (top left,  $\tau > 0.03$ ) exactly corresponds to all 1024 combinations of inputs that contain both C8+ and RIP1+ at the same time. A more thorough examination of the relationship between total and Sobol indices is currently investigated.

## 5.2 A differential system modeling population dynamics

We consider now a system of five nonlinear ordinary differential equations (ODE) modeling the dynamics of infection of a bacterial population of *E. coli* by the bacteriophage  $\lambda$  in the mouse gut, originally proposed by De Paepe et al. (2016). Lambda is a temperate phage, meaning that an infected bacterium has two opposite outcomes: either it enters the “lysogenic” phase where it retains viral DNA in a dormant phase, (it is then called a lysogen); or it enters the “lytic” phase where the virus replicates itself, eventually leading to the destruction of the host and the release of new viral particles. Lysogens continue to grow and survive normally, until a future change in external conditions may induce the lytic phase, leading to the bacterium’s demise and release of free viruses. In the model two bacterial populations exist initially:  $L$  denotes lysogens, containing the virus in a dormant phase, and  $S$  denotes “susceptible”, uninfected bacteria. Newly lysogenized susceptible

are denoted by  $S^l$ , to distinguish them from originally resident lysogens  $L$ . Once infected, susceptible bacteria enter lytic phase (variable  $Q$ ) with probability  $(1 - g)$ . As for lysogens  $L$  and  $S^l$ , they enter lytic phase at constant rate  $x$ . After some time, lytic bacteria  $Q$  die and release free viruses, denoted by variable  $V$ . The system consists in five ODE:

$$\left\{ \begin{array}{l} dL/dt = r(1 - N/k)L - xL - dL, \\ dS/dt = r(1 - N/k)S - aVS - dS, \\ dS^l/dt = r(1 - N/k)S^l - xS^l + gaVS - dS^l, \\ dQ/dt = x(L + S^l) + (1 - g)aVS - lQ - dQ, \\ dV/dt = ylQ - aV(N + Q) - dV, \end{array} \right. \quad (26)$$

where  $N$  denotes total bacterial population:  $N = L + S + S^l$ . In total, the system contains eight parameters, denoted by small letters and listed in Table 2 of the supplementary file. Viable bacterial populations  $L$ ,  $S$  and  $S^l$  grow according to the same logistic term with parameters  $r$  and  $d$ , while lytic bacteria  $Q$  do not grow. Besides induction rate  $x$  and lysogenisation probability  $g$ , key infection parameters are the burst size  $y$ , which is the average number of released free viruses after lysis, and the adsorption constant  $a$ , governing the attachment of a free virus to a bacterium. A detailed description of the parameters can be found in the original paper by De Paepe et al. (2016) and its supplementary material, along with an extensive presentation of the equations and the modeling choices behind them.

The analysis of the system was carried out in the original paper. Four equilibria exist, they are characterized by the extinction or persistence of populations  $L$  and  $S$ : first, a “wash-out” equilibrium where all microbial populations vanish; second, an equilibrium where  $L = L^* > 0$  is maintained while  $S = 0$ ; third, an equilibrium where  $S = S^* > 0$  is maintained while  $L = 0$ ; and finally, an equilibrium where both  $L = L^* > 0$  and  $S = S^* > 0$  coexist. In this analysis parameters were treated symbolically, leading to explicit formulas for equilibria as well as explicit relations between parameters determining

equilibria’s reachability. For conciseness, those explicit formulas are not reproduced here but can be found in De Paepe et al. (2016).

While this type of symbolic computations is relatively classical to analyze such systems, it is worth noting that it can rapidly become cumbersome, even impossible if the dimension is too high or if the system contains highly nonlinear terms. Here we propose to use a global sensitivity analysis as an alternative to such calculations. Although the output will necessarily be less informative than explicit formulas, in the following we show that global sensitivity indices capture interesting properties and provide valuable information about the effects of the parameters on the dynamics. Such analyses can thus become particularly helpful in the analysis of complex and large ODE systems, pointing for instance to specific groups of parameters that can be further investigated with dedicated tools.

We consider the system’s eight parameters, to which we add the initial values of populations  $L$  and  $S$ , denoted by  $L_0$  and  $S_0$ , leading to  $d = 10$  inputs. A dataset of  $n2^d = 4987 \times 1024$  model simulations was then generated, according to (10). The inputs were drawn independently from uniform or log-uniform distributions. See Table 2 of the supplementary file for details. Each simulation was carried out by the matlab routine `ode45`, until a steady state was reached. The (base 10) logarithm was applied to the obtained population values, in line with the original paper; additionally, small populations were truncated in order to avoid unwanted numerical effects. The detailed procedure can be found in Section F of the supplementary file. As before total, Sobol and Shapley indices were estimated from the dataset as in Section 3 and the computations were done with the Möbius transform and extended Möbius transform algorithms presented in Section 4. The size  $n$  was again arbitrary and initially set to 5000 but some simulations had to be discarded because of numerical anomalies (see the supplementary file for more information). In view of the obtained confidence intervals, it was assessed that no more simulations was needed.

Figure 2 presents the ten highest Sobol index estimates. A rapid inspection of those

indices shows that  $L$  is mainly impacted by parameters  $r$  and  $d$ , while  $S$  is mainly impacted by  $x$  and  $y$ . More precisely, the abundance of  $L$  is mostly dependent on the interaction between  $r$  and  $d$ , emphasized by the significantly high value of  $\sigma^*({r, d})$ . This was partly observed in De Paepe et al. (2016), as the first and second equilibria are separated according to the relative position of  $r$  and  $d$ . Parameters  $r$  and  $d$  mainly govern bacterial growth, while  $x$  and  $y$  mainly govern viral infection, therefore the fact that susceptible are more sensitive to infection than lysogens is relatively unsurprising. However, the sensitivity analysis reveals a higher importance of  $x$  and  $y$  with respect to other viral parameters such as the adsorption constant  $a$ , for instance. This was rather unexpected.

Additional observations can be made about Figure 2. First, the viral population  $V$  depends on more parameters than bacterial populations: parameters  $r$  and  $d$  suffice to contribute to more than 80% of the variance of  $N$  (Test (18) with the two highest Sobol indices  $\sigma^*({r, d})$  and  $\sigma^*({r})$  returned a p-value  $< 1.5 \times 10^{-3}$ ), whereas five parameters  $r, d, a, x$  and  $y$  are necessary to contribute to more than 80% of the variance of  $V$  (Test (18) with the five highest Sobol indices  $\sigma^*({r, d}), \sigma^*({r}), \sigma^*({a}), \sigma^*({x})$  and  $\sigma^*({y})$  returned a p-value  $< 1.5 \times 10^{-2}$ ). Interestingly, this phenomenon can be observed when looking at the explicit formulas in the original paper. Second, parameters  $S_0$  and  $L_0$ , which are part of the initial condition, only appear with significant nonzero values for variable  $S^l$ , newly lysogenized bacteria. Usually in a non-degenerate ODE system, this type of dependence should not appear: equilibria are generally independent of the initial condition. Nevertheless in the original paper, a singular property of the system was noted: rewriting (26) in the system of variables  $(N, S, S^l, Q, V)$  implies that  $S^l$  does not influence the rest of the system and can be omitted, thus dropping the dimension to 4 instead of 5. This implies that no explicit formula can be retrieved for the equilibrium of  $S^l$ , but instead for the sum  $L + S^l$ . In the sensitivity analysis, the significant effect of the initial condition on the steady state of  $S^l$  is a hint that such phenomenon may occur. Those two observations: multiple

dependencies of variable  $V$  and dependence of  $S^l$  with respect to initial conditions, illustrate the interest of using a global sensitivity analysis as a first step to study this type of dynamical systems. It becomes particularly interesting for systems where explicit formulas are unavailable.

Contrary to the previous Boolean model where interactions of inputs were relatively insignificant, here they are more relevant. We noted earlier the significance and importance of the interaction effects  $\{r, d\}$  or  $\{x, y\}$ . As a matter of fact, this system seems to exhibit a generally high influence of interactions between parameters. To quantify this, we implemented Test (17) described above. The results are presented in Figure 3. If for a singleton  $\{i\}$ , one observes a significant difference  $\tau(\{i\}) - \tau^*(\{i\})$  (grey area of the bar), then one concludes that the influence of the input  $\{i\}$  is strongly dependent on interactions with other inputs. This is notably the case for parameters  $r$  and  $d$ , which we already know from Figure 2. To a lesser extent, interaction effects are also important for other parameters as well, see Figure 3. A notable counterexample is the effect of parameter  $g$  for variable  $S^l$ . This parameter denotes the probability of lysogenisation for a newly infected bacterium. The fact that it has a high effect on the population of new lysogens is therefore expected; however, statistical testing indicates this effect is relatively isolated from other parameters, which is a new result.

## 6 Discussion

An inference method for global sensitivity analysis was designed and practically tested on two dynamical systems. Although many estimation methods already exist in the literature, they largely focus on first-order Sobol indices only, or, when interactions are considered, the asymptotic normality of the estimators is rarely considered to quantify the uncertainties of the estimates. Thus, the method designed in this paper bridges a gap in the literature: it



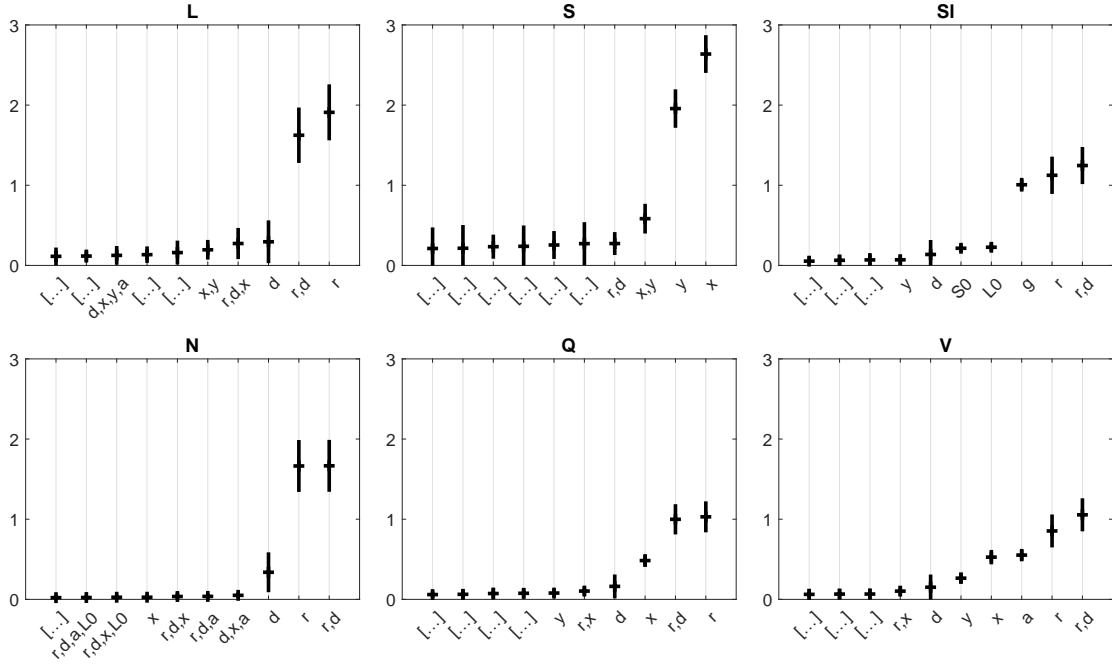


Figure 2: Ten highest Sobol index estimates of system (26) steady state (after log-transformation, see main text). Interactions containing more than 6 inputs are omitted.

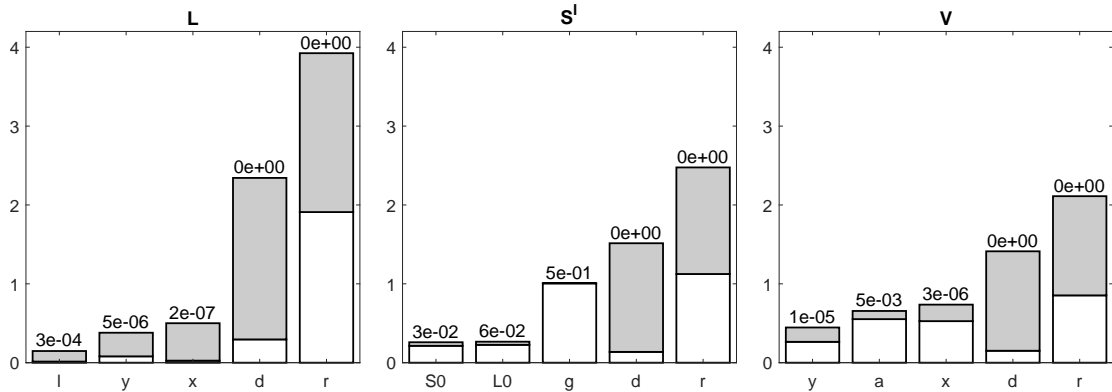


Figure 3: Importance of interactions in System (26). The bars compare  $\tau^*({i})$  (white) and  $\tau({i})$  (white+grey) for the five highest  $\tau({i})$ . P-values of test (17) indicated on top.

performs the inferences for everything thanks to the established asymptotic normality of the estimators. In particular, a procedure to test the contribution of an arbitrary number of Sobol indices of arbitrary orders was designed. To compute the estimates and their asymptotic variance-covariance matrices, the fast Möbius transform and the extended fast Möbius transform algorithms were proposed and implemented. The method is general: although total indices were used in step 1 of the method, they can be replaced by any sensitivity measure for which there is an asymptotically normal estimator.

Questions remain, however. Potential limitations and extensions are discussed below.

**Dimension of the input space.** Calculating the index estimates of all input combinations is feasible if the number of inputs is not too large. If the model runs fast, then perhaps up to a dozen inputs can be considered. Otherwise, owing to the sparsity-of-effects principle—aka Pareto principle (Becker, 2020)—it is reasonable to expect that a sufficiently large number of total indices will be close to zero. Thus, we may still apply the inference method proposed, but to a well-chosen selection of inputs. For instance, we might proceed as follows. First, we perform a screening experiment by calculating estimates of the total indices and their duals associated with individual inputs only. Second, we spot the inputs for which total index estimates are below some threshold and fix the corresponding inputs to some arbitrary values. Finally, we apply the inference method proposed to the remaining inputs only.

**Global sensitivity analysis with dependent inputs.** If the inputs are not mutually independent then the Sobol-Hoeffding decomposition presented in Section 2 no longer holds and hence Sobol indices are undefined. Interpretation of the right-hand side of (6) remains valid whether or not the inputs are mutually independent: in either case, it is the output variance induced by a random change in  $X_A$ , averaged over all the remaining inputs. Therefore, we can *define*  $\tau(A)$  through (6) and, in turn,

define and calculate Sobol indices through the identity  $\tau(D) - \tau(A) = \tau^*(D \setminus A)$  and the Möbius inversion formula (13), respectively. The inference method of Section 3 remains valid as long as we have an asymptotically normal estimator of the vector of total indices. The estimator given in Section 3.1 cannot be used anymore but one may use, adapt and/or extend other estimation methods (Da Veiga et al., 2023; Gamboa et al., 2022).

**Improving the efficiency of estimators.** Computational aspects and efficiency of estimators are intimately connected in sensitivity analysis: building more efficient estimators leads to computational savings, since we need less data for a given level of precision. To this aim, it might be interesting to consider adaptive estimation as in Broto et al. (2020). Quasi-Monte Carlo samples may also improve estimates, although controlling the statistical error is more difficult.

## Acknowledgments

We thank two anonymous reviewers and an associate editor for very detailed and constructive comments that led to an improved version of this manuscript.

## SUPPLEMENTARY MATERIAL

**Supplementary file:** supplementary material for the main text (.pdf file).

**Code:** MATLAB code to compute the estimates of the total, dual and Sobol indices, and the Shapley effects, as well as all the variance-covariance matrices, with the fast and extended fast Möbius transform algorithms (.m files).

**Datasets:** Datasets of outputs from the two models (.mat files).

## References

- Azzini, I., T. A. Mara, and R. Rosati (2021). Comparison of two sets of Monte Carlo estimators of Sobol’ indices. *Environmental Modelling & Software* 144, 105167.
- Ball, P. (2023). *How life works: a user’s guide to the new biology*. Chicago: The University of Chicago Press.
- Becker, W. (2020). Metafunctions for benchmarking in sensitivity analysis. *Reliability Engineering & System Safety* 204, 107189.
- Bénard, C., G. Biau, S. Da Veiga, and E. Scornet (2022). Shaff: Fast and consistent shapley effect estimates via random forests. In G. Camps-Valls, F. J. R. Ruiz, and I. Valera (Eds.), *Proceedings of The 25th International Conference on Artificial Intelligence and Statistics*, Volume 151 of *Proceedings of Machine Learning Research*, pp. 5563–5582. PMLR.
- Björklund, A., T. Husfeldt, P. Kaski, and M. Koivisto (2007). Fourier meets Möbius: fast subset convolution. In *Proc. of the 39th ACM symposium on Theory of computing*, pp. 67–74.
- Boyle, E. A., Y. I. Li, and J. K. Pritchard (2017). An Expanded View of Complex Traits: From Polygenic to Omnigenic. *Cell* 169(7), 1177–1186.
- Broto, B., F. Bachoc, and M. Depecker (2020). Variance Reduction for Estimation of Shapley Effects and Adaptation to Unknown Input Distribution. *SIAM/ASA Journal on Uncertainty Quantification* 8(2), 693–716.
- Calzone, L., L. Tournier, S. Fourquet, D. Thieffry, B. Zhivotovsky, E. Barillot, and A. Zinovyev (2010). Mathematical modelling of cell-fate decision in response to death receptor engagement. *PLoS Computational Biology* 6(3), e1000702.

- Castro, J., D. Gómez, and J. Tejada (2009). Polynomial calculation of the Shapley value based on sampling. *Computers & Operations Research* 36(5), 1726–1730.
- Da Veiga, S. and F. Gamboa (2013). Efficient estimation of sensitivity indices. *Journal of Nonparametric Statistics* 25(3), 573–595.
- Da Veiga, S., F. Gamboa, A. Lagnoux, T. Klein, and C. Prieur (2023). New estimation of Sobol’indices using kernels. *arXiv preprint arXiv:2303.17832*.
- Dayar, T. and M. C. Orhan (2015). On Vector-Kronecker Product Multiplication with Rectangular Factors. *SIAM Journal on Scientific Computing* 37(5), S526–S543.
- De Paepe, M., L. Tournier, E. Moncaut, O. Son, P. Langella, and M.-A. Petit (2016). Carriage of  $\lambda$  latent virus is costly for its bacterial host due to frequent reactivation in monoxenic mouse intestine. *PLoS Genetics* 12(2), e1005861.
- Fernandes, P., B. Plateau, and W. J. Stewart (1998). Efficient descriptor-vector multiplications in stochastic automata networks. *Journal of the ACM* 45(3), 381–414.
- Funaki, Y. (1998). Dual axiomatizations of solutions of cooperative games.
- Gamboa, F., P. Gremaud, T. Klein, and A. Lagnoux (2022). Global sensitivity analysis: A novel generation of mighty estimators based on rank statistics. *Bernoulli* 28(4), 2345–2374.
- Gamboa, F., A. Janon, T. Klein, A. Lagnoux, and C. Prieur (2016). Statistical inference for Sobol pick-freeze Monte Carlo method. *Statistics* 50(4), 881–902.
- Gamboa, F., T. Klein, A. Lagnoux, and L. Moreno (2021). Sensitivity analysis in general metric spaces. *Reliability Engineering & System Safety* 212, 107611.

- Gilquin, L., E. Arnaud, C. Prieur, and A. Janon (2019). Making the best use of permutations to compute sensitivity indices with replicated orthogonal arrays. *Reliability Engineering & System Safety* 187, 28–39.
- Goda, T. (2021). A simple algorithm for global sensitivity analysis with Shapley effects. *Reliability Engineering & System Safety* 213, 107702.
- Grabisch, M., J.-L. Marichal, and M. Roubens (2000). Equivalent Representations of Set Functions. *Mathematics of Operations Research* 25(2), 157–178.
- Harsanyi, J. C. (1963). A Simplified Bargaining Model for the n-Person Cooperative Game. *International Economic Review* 4(2), 194–220.
- Herin, M., M. Il Idrissi, V. Chabridon, and B. Iooss (2024). Proportional marginal effects for global sensitivity analysis. *SIAM/ASA Journal on Uncertainty Quantification* 12(2), 667–692.
- Hoeffding, W. (1948). A class of statistics with asymptotically normal distribution. *The Annals of Mathematical Statistics* 19(3), 293–325.
- Homma, T. and A. Saltelli (1996). Importance measures in global sensitivity analysis of nonlinear models. *Reliability Engineering & System Safety* 52(1), 1–17.
- Il Idrissi, M., N. Bousquet, F. Gamboa, B. Iooss, and J.-M. Loubes (2023). On the coalitional decomposition of parameters of interest. *Comptes Rendus. Mathématique* 361, 1653–1662.
- Iman, R. L. and S. C. Hora (1990). A robust measure of uncertainty importance for use in fault tree system analysis. *Risk Analysis* 10(3), 401–406.
- Iooss, B. and C. Prieur (2019). Shapley effects for sensitivity analysis with correlated inputs:

- Comparisons with Sobol' indices, numerical estimation and applications. *International Journal for Uncertainty Quantification* 9(5).
- Iooss, B., S. D. Veiga, A. Janon, G. Pujol, with contributions from Baptiste Broto, K. Boumhaout, T. Delage, R. E. Amri, J. Fruth, L. rent Gilquin, J. Guillaume, L. L. Gratiot, P. Lemaitre, A. Marrel, A. Mey-naoui, B. L. Nelson, F. ippo Monari, R. Oomen, O. Rakovec, B. Ramos, O. Roustant, E. hye Song, J. Staum, R. Sueur, T. Touati, and F. Weber (2020). *sensitivity*. R package version 1.23.0.
- Janon, A., T. Klein, A. Lagnoux, M. Nodet, and C. Prieur (2014). Asymptotic normality and efficiency of two Sobol index estimators. *ESAIM: Probability and Statistics* 18, 342–364.
- Jansen, M. J. (1999). Analysis of variance designs for model output. *Computer Physics Communications* 117(1), 35–43.
- Janssen, P. (1994). Assessing sensitivities and uncertainties in models: a critical evaluation. In J. Grasman and G. van Straten (Eds.), *Predictability and Nonlinear Modelling in Natural Sciences and Economics*. Springer.
- Kennes, R. (1992). Computational aspects of the Mobius transformation of graphs. *IEEE Transactions on Systems, Man, and Cybernetics* 22(2), 201–223.
- Knuth, D. E. (1997). *The art of computer programming*. Addison Wesley Longman. Volume 1. Fundamental Algorithms.
- Kucherenko, S. and S. Song (2017). Different numerical estimators for main effect global sensitivity indices. *Reliability Engineering and System Safety* 165, 222–238.
- La Haye, R. (2009). Binary relations on the power set of an  $n$ -element set. *Journal of Integer Sequences* 12(2), 3.

- Liu, R. and A. B. Owen (2006). Estimating mean dimensionality of analysis of variance decompositions. *Journal of the American Statistical Association* 101(474), 712–721.
- Oishi, T., M. Nakayama, T. Hokari, and Y. Funaki (2016). Duality and anti-duality in TU games applied to solutions, axioms, and axiomatizations. *Journal of Mathematical Economics* 63, 44–53.
- Owen, A. B. (2013). Better estimation of small Sobol’ sensitivity indices. *ACM Transactions on Modeling and Computer Simulation (TOMACS)* 23(2), 1–17.
- Owen, A. B. (2014). Sobol’ Indices and Shapley Value. *SIAM/ASA Journal on Uncertainty Quantification* 2(1), 245–251.
- Owen, A. B. and C. Prieur (2017). On Shapley Value for Measuring Importance of Dependent Inputs. *SIAM/ASA Journal on Uncertainty Quantification* 5(1), 986–1002.
- Piano, S. L., F. Ferretti, A. Puy, D. Albrecht, and A. Saltelli (2021). Variance-based sensitivity analysis: The quest for better estimators and designs between explorativity and economy. *Reliability Engineering and System Safety* 206, 107300.
- Plischke, E., E. Borgonovo, and C. L. Smith (2013). Global sensitivity measures from given data. *European Journal of Operational Research* 226(3), 536–550.
- Plischke, E., G. Rabitti, and E. Borgonovo (2021). Computing Shapley effects for sensitivity analysis. *SIAM/ASA Journal on Uncertainty Quantification* 9(4), 1411–1437.
- Prieur, C. and S. Tarantola (2015). Variance-based sensitivity analysis: theory and estimation algorithms. In *Handbook of Uncertainty Quantification*, pp. 1–23. Springer.
- Rota, G.-C. (1964). On the Foundations of Combinatorial Theory I. Theory of Mobius Functions. *Z. Wahrscheinlichkeitstheorie* 2, 340–368.



- Saltelli, A. (2002). Making best use of model evaluations to compute sensitivity indices. *Computer Physics Communications* 145(2), 280–297.
- Saltelli, A., P. Annoni, I. Azzini, F. Campolongo, M. Ratto, and S. Tarantola (2010). Variance based sensitivity analysis of model output. Design and estimator for the total sensitivity index. *Computer Physics Communications* 181, 259–270.
- Saltelli, A., M. Ratto, T. Andres, F. Campolongo, J. Cariboni, D. Gatelli, M. Saisana, and S. Tarantola (2008). *Global Sensitivity Analysis. The Primer*. Wiley.
- Saltelli, A., S. Tarantola, and F. Campolongo (2000). Sensitivity analysis as an ingredient of modeling. *Statistical Science* 15(4), 377–395.
- Saltelli, A., S. Tarantola, and K. P.-S. Chan (1999). A quantitative model-independent method for global sensitivity analysis of model output. *Technometrics* 41(1), 39–56.
- Shapley, L. S. (1951). The value of an n-person game. Technical report, RAND CORP SANTA MONICA CA. Technical Report.
- Sobol, I. M. (1993). Sensitivity estimates for nonlinear mathematical models. *Mathematical modelling and computational experiments* 1(4), 407–414.
- Sobol, I. M. and Y. L. Levitan (1999). On the use of variance reducing multipliers in Monte Carlo computations of a global sensitivity index. *Computer Physics Communications* 117(1), 52–61.
- Solís, M. (2019). Non-parametric estimation of the first-order Sobol indices with bootstrap bandwidth. *Communications in Statistics-Simulation and Computation* 50(9), 2497–2512.
- Song, E., B. L. Nelson, and J. Staum (2016). Shapley Effects for Global Sensitivity Analysis:

- Theory and Computation. *SIAM/ASA Journal on Uncertainty Quantification* 4(1), 1060–1083.
- Sudret, B. (2008). Global sensitivity analysis using polynomial chaos expansions. *Reliability Engineering & System Safety* 93, 964–979.
- Tissot, J.-Y. and C. Prieur (2015). A randomized orthogonal array-based procedure for the estimation of first- and second-order Sobol’ indices. *Journal of Statistical Computation and Simulation* 85(7), 1358–1381.
- Tournier, L. and M. Chaves (2009). Uncovering operational interactions in genetic networks using asynchronous Boolean dynamics. *Journal of Theoretical Biology* 260(2), 196–209.
- van der Vaart, A. W. (1998). *Asymptotic Statistics*. Cambridge University Press.
- Winter, E. (2002). The Shapley value. In *Handbook of Game Theory with Economic Applications*, Volume 3, pp. 2025–2054. Elsevier.
- Yates, F. (1937). *The design and analysis of factorial experiments*. Harpenden: Imperial Bureau of Soil Science.
- Zinovyev, A., S. Fourquet, L. Tournier, L. Calzone, and E. Barillot (2012). Cell death and life in cancer: mathematical modeling of cell fate decisions. In *Advances in Systems Biology*, pp. 261–274. Springer.