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Variance-based sensitivity analysis for stochastic chemical kinetics

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Summary

Sensitivity analysis is a process of computing sensitivity indices, which are certain measures of importance of parameters in influencing the outputs of mathematical models. Sensitivity indices computed in variance-based sensitivity analysis yield quantitative answers to questions like how much on average the variance of model output, measuring its uncertainty, decreases, if exact values of certain unknown parameters are determined, e. g. in an experiment. We propose new schemes for estimation of variance-based sensitivity indices of outputs of stochastic models, their conditional expectations and histograms given the parameters. Unbiased estimators obtained in these schemes can be used in a Monte Carlo (MC) procedure approximating sensitivity indices. We derive relations between variances of final estimators of MC procedures making the same number of evaluations of given function, but using different schemes, both for the newly introduced schemes and for some used before in the literature. Numerical experiment for a discrete state stochastic Markov model of a chemical reaction network (DM) shows that our method can lead to much lower error than method analogous to the one offered by Degasperi et al. [13]. Further numerical experiments demonstrate that the application of random time change (RTC) algorithm due to Rathinam et al. for simulation of DM can lead to over 30 times lower variance of estimators of certain sensitivity indices than when Gillespie's direct (GD) method is used, and that this variance may significantly depend on the order of reactions in GD method. We provide some intuitions explaining these effects. We generalize measures used for comparing dispersion of different distributions, such as coefficient of variation and Fano factor to the random parameters case, in a way that they can be computed along with variance-based sensitivity indices. The methods proposed in this work are general and can be used for variance-based sensitivity analysis of stochastic models in any discipline.

Tytuł pracy w języku polskim

Oparta o wariancję analiza wrażliwości stochastycznych modeli reakcji chemicznych

Streszczenie w języku polskim

Analiza wrażliwości to proces obliczania współczynników wrażliwości, które są pewnymi miarami ważności parametrów pod względem ich wpływu na wyniki modeli matematycznych. Współczynniki wrażliwości obliczane w analizie wrażliwości opartej o wariancję dostarczają ilościowych odpowiedzi pytania takie jak np. o ile średnio zmniejszy się wariancja wyników modelu, mierząca ich niepewność, jeśli wyznaczymy dokładne wartości niektórych nieznanych parametrów, np. doświadczalnie. Proponujemy nowe schematy do estymacji opartych o wariancję współczynników wrażliwości wyników modeli stochastycznych, ich warunkowych wartości oczekiwanych i histogramów względem parametrów. Nieobciążone estymatory otrzymywane w tych schematach mogą zostać wykorzystane w procedurze Monte Carlo (MC) aproksymującej współczynniki wrażliwości. Wyznaczamy relacje między wariancjami końcowych estymatorów procedur MC wykonujących tyle samo ewaluacji danej funkcji ale używając różnych schematów, zarówno dla nowo podanych schematów, jak i pewnych dotychczas używanych w literaturze. Eksperyment numeryczny dla dyskretnego Markowskiego modelu układu reakcji chemicznych (DM) pokazuje, że

nasza metoda może prowadzić do o wiele mniejszych błędów niż metoda zaproponowana przez Degasperiego i innych [13]. Dalsze eksperymenty numeryczne pokazują, że użycie algorytmu random time change (RTC) zaproponowanego przez Rathinama i innych do symulacji DM może prowadzić do ponad 30-krotnie mniejszej wariancji estymatorów pewnych współczynników wrażliwości, niż metoda Gillespie's direct (GD) i że wariancja ta może się bardzo zmieniać wraz ze zmianą kolejności reakcji w metodzie GD. Dostarczamy pewnych intuicji wyjaśniających te efekty. Uogólniamy miary służące do porównywania rozrzutu różnych rozkładów, jak na przykład współczynnik zmienności (ang. coefficient of variation), czy współczynnik Fano na przypadek losowych parametrów, w taki sposób, że mogą one być obliczane równocześnie ze współczynnikami wrażliwości opartymi o wariancję. Metody zaproponowane w tej pracy są ogólne i mogą zostać zastosowane do analizy wrażliwości opartej o wariancję modeli stochastycznych w różnych dziedzinach.

Key words

variance-based sensitivity analysis, stochastic simulations, Gillespie's direct method, Monte Carlo, Markov process, chemical reaction

Słowa kluczowe

analiza wrażliwości oparta o wariancję, symulacje stochastyczne, Gillespie's direct method, Monte Carlo, proces Markowa, reakcja chemiczna

Area of study (codes according to Erasmus Subject Area Codes List)

11.2 Statistics

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Introduction

Mathematical models often take some parameters as inputs and return some results, which we call outputs of the model, and which are certain functions of the inputs. For instance in popular ordinary differential equations based models [3] in chemical reaction kinetics the parameters can be initial concentrations of reacting species and reaction rate constants, while the output can be concentration of any species at a given time. Many physical systems, such as chemical reaction networks involving small concentrations of certain species, are well described by stochastic models [45, 60]. It is for instance becoming clear that such models can successfully describe the functioning of a number of important biochemical systems, including certain gene regulatory networks [38, 48] and signaling pathways [34, 57]. The output of a stochastic model with given parameters is usually not a single value but random variable with distribution specified by the parameters. Well-stirred chemical reaction networks with small numbers of certain particles are often described using discrete stochastic Markov model (DM), the history of which is reviewed in [40]. The inputs of DM can be reaction rates and some parameters describing initial distributions of particles and the output might be for instance the random number of particles at a given time. A number of other stochastic formalisms of chemical kinetics have also been used such as chemical Langevin equation or hybrid stochastic-deterministic models [45], the latter being particularly useful for modelling reactions with both small and large concentrations of different species.

Sensitivity analysis methods are concerned with computing different measures of relative importance of arguments in influencing the value of a function, and in particular can be applied to outputs and inputs of mathematical models. In stochastic models parameters of distribution of the output like mean [49], variance [4] or histograms [13] are often taken as functions whose sensitivity indices with respect to model inputs are computed. Sensitivity analysis has found applications in such diverse fields as chemical kinetics [47, 59, 53, 61], nuclear safety [27], environmental science [56] or molecular dynamics [9]. In chemical kinetics sensitivity analysis has been used among others for parameter estimation [30, 29], and model simplification [10, 42, 35, 14]. Main types of sensitivity analysis methods are local and global ones. Local sensitivity analysis methods deal with approximating derivatives of the function with respect to its arguments in a given point of the parameter space. A number of attempts were made to speed up the approximation of these derivatives for DM [49, 46]. In particular Rathinam et al. [49] showed that using random time change (RTC) algorithm, which is based on the representation of discrete Markov processes due to Kurtz [18], may lead to much lower variance of estimators of finite difference of mean values of particle numbers at a given time, than when Gillespie's direct (GD) method is used.

In global sensitivity analysis the arguments of a function are considered to be random variables. They might be for instance results of uncertain measurements of some rate constants. Global sensitivity analysis methods provide measures of importance of parameters in influencing the value of a function over the whole range of their possible values. Variance-based sensitivity analysis is a well established type of global sensitivity analysis, which has a long history of being used in chemical kinetics, its first formulation known as FAST method having been introduced for this purpose in the seventies [52, 11]. Importance indices provided by variance-based sensitivity analysis yield quantitative answers to ques-

tions which might serve as reasons for undertaking the analysis. Some of these questions are what average reduction of variance and thus improvement of precision of the model can be achieved if some of the unknown constants are determined by a precise measurement [52], or what average error is caused by fixing a parameter for instance to simplify the model [55]. Variance-based sensitivity analysis has been used among others for parameter estimation in a linear compartmental model [29], and was demonstrated useful for reducing a model of a certain stage of production of an anti parasitic medicine Ivermectin [10].

The only work so far, in which variance-based sensitivity analysis was performed for parameters of distribution of outputs of stochastic models, was a paper by Degasperi et al. [13]. Authors performed simulations in every point of a grid in the parameter space to approximate conditional histograms given the parameters. Unfortunately, the generalization of variance to the case of vector-valued functions they used causes basic properties of variance-based sensitivity indices, crucial for their certain applications, to be lost. Furthermore, their method provides no error estimates for the results.

We propose how to generalize variance to vector-valued functions, like conditional histograms, so that interpretations of variance-based sensitivity indices hold. We introduce the concept of a scheme for estimation of sensitivity index, containing among others the information of an unbiased estimator for the index and the number of function evaluations needed to compute it. We propose different schemes for estimation of variance-based sensitivity indices of conditional expectations and histograms of outputs of stochastic models given the parameters, which can be used to compute estimators in each step of Monte Carlo (MC) procedure. Thus we can obtain not only estimates of the indices, but also estimates of error of the result, that is of variance of final MC estimator. We introduce inefficiency constant of a scheme in estimating given index equal to variance of estimator given by the scheme times the number of function evaluations used to compute it. Ratio of such constants for two different schemes is equal to the ratio of variances of final MC estimators using these schemes and the same number of evaluations of a given function with certain distribution of its parameters. Thus if function evaluations are the main cost of MC step, as is in case of our experiments, these constants can be used to compare error resulting from using different schemes for the same computation time. We derive relations between inefficiency constants for different schemes, both the ones already used to deterministic chemical models in the literature and the ones introduced in this work.

Numerical experiments on example for which analytic values of sensitivity indices can be obtained demonstrate better performance of our method in comparison to a method analogous to Degasperi's et al. in computing sensitivity indices of conditional means, and the fact that quasi-Monte Carlo can lead to speed-up in computation of some indices. Further numerical experiments demonstrate that using random time change (RTC) algorithm can lead to lower variance of certain estimators computed in our schemes, than when Gillespie's direct method (GD) is used. We also show that this variance is influenced by order of reactions used in GD method and give some intuitions concerning possible reasons for this dependence. Along with sensitivity indices we compute newly introduced generalizations of measures of dispersion of distribution of outputs of stochastic models to the random parameters case.

The rest of this work is organized as follows. In Chapter 1 we define chemical reaction network, define DM for the constant parameters case and provide its constructions. In Chapter 2 we discuss possible interpretations of random parameters in models and extend DM construction to the random parameters case. In Chapter 3 we define variance-based sensitivity indices and describe their interpretations as well as possible applications. In Chapter 4 we define and provide schemes for estimation of sensitivity indices, define their inefficiency constants and derive relations between them. We also discuss implementation details, introduce method analogous to Degasperi's et al. and method depending on using quasi-Monte Carlo sampling in the parameter space. Chapter 5 is devoted to numerical experiments.

We assume basic knowledge of the reader about probability theory, such as contained in the first Chapter of [15]. More advanced definitions and theorems as well as assumptions we are making throughout the text are given or referenced to in the main text or Appendix A.

Chapter 1

Stochastic chemical models with constant parameters

1.1. Chemical reaction network

A chemical reaction network contains N chemical species with symbols X_1, \dots, X_N . In DM formalism the state of the system at a given moment is characterized by a vector of natural numbers $x = (x_1, \dots, x_N)$ from some set of admissible states $E \subset \mathbb{N}^N$. Coordinates of x describe the numbers of species of each kind. L chemical reactions (R_1, \dots, R_L) can occur. The l -th reaction is described by formula



Vector $\underline{s}_l = (\underline{s}_{l,i})_{i=1}^N$ is called the stoichiometric vector of reactants and $\bar{s}_l = (\bar{s}_{l,i})_{i=1}^N$ of products of reaction R_l . In all this work we denote $I_n = \{1, \dots, n\}$. We require that $\underline{s}_l \geq 0$, which means $\underline{s}_{l,i} \geq 0$ for $i \in I_N$ and similarly $\bar{s}_l \geq 0$. We define transition vector as $s_l = \bar{s}_l - \underline{s}_l$. Occurrence of l -th reaction makes the system at state x to transition to state $x + s_l$. With every reaction R_l is associated a propensity $a_l(k)(x)$ - a non negative function of state $x \in E$ and real vector k , called (vector of) rate constants, which can have values in some set $S_k \subset \mathbb{R}^{n_k}$ for certain n_k natural positive. Intuitively speaking, propensity describes how quickly reaction is proceeding in state x . For propensities in DM we require that $a_l(k)(x) = 0$ if for some $i \in I_n$ $x_i < \underline{s}_i$, that is if there are too few particles of certain reactant in the system for the reaction to happen. For instance in the stochastic version of mass action kinetics [18] we take $k = (k_i)_{i=1}^L$ and

$$a_l(k)(x) = k_l \binom{x}{\underline{s}_l}, \quad (1.2)$$

where $\binom{x}{\underline{s}_l} = \prod_{i=1}^N \binom{x_i}{\underline{s}_{l,i}}$ is the number of possible ways in which the reactants can collide for the l -th reaction to occur, and k_l is called the rate constant of this reaction. Formally, we describe chemical reaction R_l as a triple, which is a function of the rate constants

$$R_l(k) = (a_l(k)(x), \underline{s}_l, \bar{s}_l), \quad (1.3)$$

and chemical reaction network RN as a tuple containing sequence of reactions and the set of species

$$RN(k) = ((R_l)_{l=1}^L, \{X_1, \dots, X_N\}), \quad (1.4)$$

also being a function of the rate constants. A reverse reaction to a given is one in which stoichiometric vectors of reactants and products are replaced. We say that reaction is reversible if both the reaction and its reverse are present in the reaction network.

1.2. Discrete stochastic model with constant parameters

We define stochastic chemical reaction network with constant parameters $p = (c, k)$ (DMCP) as a certain Markov process on E with allowed times $T = [0, \infty)$, which is a type of right-continuous stochastic process [41]. Shortly, stochastic process Y with values in E and allowed times T is a family of random variables $(Y_t)_{t \in T}$ with values in E . One can treat Y as a random variable whose values, known as trajectories of the process, are elements of E^T [5]. Right-continuous process is one that behaves as follows. It starts in some state $Z_0 \in E$, where it waits for time period S_0 at the end of which it transitions to another state Z_1 , where it waits for another time S_1 and so on for some discrete process $(Z_i)_{i \geq 0}$, known as jump process of Y and $(S_i)_{i \geq 0}$ known as its holding times of Y (see [41] for precise definitions). The moment

$$\chi = \sum_{i=0}^{\infty} S_i, \quad (1.5)$$

when a process makes infinitely many jumps for the first time is called its explosion time. If $\chi = \infty$, that is no infinite number of transitions can occur in finite time, we call the process nonexplosive. Since in our case transition corresponds to firing of a reaction and it is nonphysical for infinite number of reactions to occur in finite time we require the process to be nonexplosive. A right-continuous nonexplosive stochastic process is uniquely defined by its jump chain and holding times. An important property of stochastic process Y is its distribution defined similarly as for random variable [5]. The distribution of a Markov process is defined by its distribution at time 0 and non negative numbers $q_{x,y}$ for $x, y \in E$, $x \neq y$ known as intensities of going from state x to y , fulfilling

$$\forall x \in E \quad \sum_{y \in E} q_{x,y} < \infty. \quad (1.6)$$

By DMCP with parameters $p = (c, k)$ and corresponding to a given chemical reaction network RN we mean a nonexplosive Markov process on E with deterministic initial distribution δ_c and intensities for $x, y \in E$, $x \neq y$, equal to

$$q_{x,y} = \sum_{l: y=x+s_l} a_l(k)(x). \quad (1.7)$$

Unfortunately, not for all reaction networks and values of parameters p DMCP exists [1]. We give some sufficient conditions in the next Section. The vector of parameters $p = (k, c)$ of DMCP corresponding to a given chemical reaction network RN uniquely determines its distribution, which we denote $\mu_{DMCP}(RN(k), c)$. One can model reaction networks using other types of processes whose distributions can also be specified using certain parameters. For instance for the chemical Langevin equation [62] such parameter vector $p = (c, k)$ would contain initial species concentrations c instead of species numbers. One can also consider models incorporating different types of events during the simulation, whose distribution depends on some additional parameters characterizing these events. For instance in the numerical simulations of the stimulation of NF- κ B regulatory network in [34] with tumor necrosis factor-alpha (TNF- α) one could consider the dose of TNF- α used for stimulation or the time when the stimulation begins as such additional parameters.

1.3. Constructions of DMCP

We show two possible constructions of DMCP with constant parameters $p = (c, k)$ corresponding to a given reaction network RN (1.4), assuming that any such process exists. The first one is based on GD method introduced in [23] and the second is based on RTC algorithm introduced in [49] and is equivalent to random time change representation of

Markov processes due to Kurtz [18]. In both constructions we inductively define the jump chain $(Z_n)_{n \geq 0}$ and holding times $(S_n)_{n \geq 1}$. Notation $X \sim U(0, 1)$ means random variable X has distribution $U(0, 1)$, which in this case means uniform on the interval $[0, 1]$. $\text{Exp}(1)$ means exponential distribution with parameter 1 [41]. Notation $X \sim Y$ means that random variables X and Y have the same distribution.

Construction 1 (GD construction). *Let U_1, U_2, \dots be independent identically distributed (i. i. d) random variables, $U_1 \sim U(0, 1)$, and T_1, T_2, \dots i. i. d. $T_1 \sim \text{Exp}(1)$. Let us assume that Z_i, S_i are defined for some $i \geq 0$. We set*

$$q := \sum_{l=1}^L a_l(k)(Z_i).$$

If $q = 0$, then we place

$$S_{i+1} := \infty, \quad Z_{i+1} := Z_i.$$

Otherwise, we set

$$S_{i+1} := \frac{T_{i+1}}{q}$$

and for

$$l = \min\{m \in I_L : \frac{1}{q} \sum_{n=1}^m a_n(k)(Z_i) \geq U_i\}$$

we place

$$Z_{i+1} = x + s_l.$$

For a given chemical reaction network and value of rate constants k we denote $A(k)(x) = \{l \in I_L : a_l(k)(x) > 0\} = \{l_1, \dots, l_{L(x)}\}$ - the set of $L(x)$ indices of reactions which can occur in state x .

Construction 2 (RTC construction). *Let us consider L independent Poisson processes $(N_l)_{l=1}^L$ with unit rates. The second construction tries to find the solution of the following integral equation*

$$Y_t = c + \sum_{l=1}^L s_l N_l \left(\int_0^t a_l(k)(Y_s) ds \right). \quad (1.8)$$

Let the i -th call of function $N_l.\text{next}$ return the i -th holding time of the Poisson process N_l . We set for $l \in I_L$

$$\tau_{0,l} := N_l.\text{next}.$$

Let us assume that Z_i, S_i and $\{\tau_{i,l}\}_{l \in I_L}$ for some $i \geq 0$ were already defined. We set

$$S_{i+1} := \min_{l \in A(k)(Z_i)} \left\{ \frac{\tau_{i,l}}{a_l(k)(Z_i)} \right\}. \quad (1.9)$$

For a certain l realizing the above minimum, we place

$$Z_{i+1} := Z_i + s_l, \quad \tau_{i+1,l} = N_l.\text{next}. \quad (1.10)$$

For $m \in A(k)(Z_i)$, $m \neq l$, we place

$$\tau_{m,i+1} := \tau_{m,i} - a_l(k)(Z_i) S_{i+1}$$

and for the remaining reaction indices $l \notin A(k)(Z_i)$ we set

$$\tau_{l,i+1} := \tau_{l,i}.$$

Above constructions define the process up to explosion time χ (1.5). When $\chi < \infty$ for the jump times defined by any of the above constructions, then we replace trajectory of the process by a trajectory constantly equal to some $c_1 \in E$, so that we receive a nonexplosive right-continuous process. Such constructed process is DMCP only if probability of event $\chi < \infty$, which is always equal for the above constructions, is also equal to 0. We then say that reaction network RN and parameters p admit DMCP. An easy criterion for RN and p to admit DMCP is given by the following Theorem.

Theorem 1. *Using notations as in Section 1.1 let us assume that for a reaction network RN and parameters $p = (c, k)$ there exist vector $m = (m_i)_{i=1}^N \in \mathbb{R}^N$ with positive coordinates, such that for $L_m = \{l \in I_L : s_l m > 0\}$ it holds*

$$A = \sup\{a_l(k)(x) : x \in E, l \in L_m\} < \infty, \quad (1.11)$$

where by $s_l m$ we mean standard scalar product of vectors. Then RN and p admit DMCP.

Vector m can be often taken to be vector of masses of each species, hence the notation.

Proof. From continuity from below (see [15] Chap. 1 Ex. 1.1) it is sufficient to show that $\mathbb{P}(\chi < t) = 0$ for every $t > 0$. Let us consider a helper process Y_t , which is created by running RTC construction with initial state c and after the explosion setting the state of the process to some vector c_1 . Similarly as in the proof of Theorem 2.7.1 in [41] one shows that if $\mathbb{P}(\chi < t) > 0$, then Y_t should take infinite number of values before time t with nonzero probability. But since for every $M > 0$ the set $\{x \in \mathbb{N}^N : mx < M\}$ is finite then also process M_t defined as

$$M_t := mY_t \quad (1.12)$$

should take infinitely many values before time t with nonzero probability. Denoting

$$s_m = \max\{s_l m : l \in I_L\} \quad (1.13)$$

we have from (1.8)

$$M_t = mY_t \leq m(c + c_1) + \sum_{l=1}^L s_m N_l(tA) = m(c + c_1) + s_m N_{LtA}, \quad (1.14)$$

where N_{LtA} is certain Poisson process with rate LtA [41]. Since Poisson processes take finite number of values in finite time with probability 1, the Theorem is proved. \square

From now on, we consider the step of rejecting trajectories for which $\chi < \infty$ and replacing it by some arbitrary constant from E to be integral part of the above constructions. Note that in all constructions of processes used for computer simulations one uses some collection of random variables R to generate the random trajectories of the process. For example for the first construction of DMCP we have $R_1 = (U_i, T_i)_{i \geq 0}$, while for the second one $R_2 = (N_i)_{i=1}^L$. We call R artificial noise variable, since it is a stochastic process which represents no physical quantity and may be even different for different constructions of the same model. Using certain construction of a process one can define function h for which

$$h(p, R) \quad (1.15)$$

is a stochastic process created by this construction with parameters p and the artificial noise R . For all values of parameters processes given by constructions 1 and 2 have the same distributions, which can be expressed using their respective functions $(h_i)_{i=1}^2$ and artificial noise terms $(R_i)_{i=1}^2$ as

$$h_1(p, R_1) \sim h_2(p, R_2) \sim \mu_{DMCP}(RN(k), c). \quad (1.16)$$

There are also other constructions equivalent to GD method, such as Gillespie first reaction method [23], Gibson and Bruck's next reaction method [22], for which (1.16) also holds, but for a different function h or artificial noise variable.

Chapter 2

Models with random parameters

2.1. Random parameters

There are many situations when we may want to treat the parameters of models as random variables $P = (P_1, \dots, P_N)$, rather than constants. These variables can for instance represent uncertain quantities. One often distinguishes 2 types of such variables (see [12] and [25] sec. 7.1 for more detailed descriptions and reviews of history of this distinction).

- Stochastic or aleatory: they are changeable in the model, like initial numbers of particles of a species in the equilibrium distribution of a stochastic model. The uncertainty associated with distribution of this variable, measured for instance by its variance, is also known as irreducible [25], since it cannot be reduced by gaining further knowledge about the model.
- Epistemic: they are also known as state of knowledge or subjective [25], since their distribution represents modeller's best judgement about their possible values. Reaction rates can often be considered to be of this kind. The judgement can be based on different values available in the literature [29] or on the fact that model with parameters from given range well describes certain experimental data [54]. Uncertainty associated with distribution of these variables has been called reducible [25], since it can be reduced if we gain more knowledge about the model, e. g. we can get to know the values of rate constants by measuring them.

Different parameters may need to be considered not independent for a given model to be realistic. For many types of DM numbers of particles of different species in the equilibrium distribution are not independent [28]. Another example are kinetic rates in chemical reaction networks containing cycles of reversible reactions which are modelled by stochastic or deterministic mass action kinetics. One often requires that the product of reaction rates in one direction of such cycle is equal to the product of rates in the reverse direction. This is known as detailed balance or Wegscheider's [16] condition and can be intuitively explained by time-reversal symmetry of chemical systems containing such reaction cycles and being in thermodynamic equilibrium [43]. However, for the purpose of efficient computation of variance-based sensitivity indices and for some interpretations of these indices to hold we need the parameters considered for sensitivity analysis to be independent. For kinetic rates this can be achieved for instance by treating some of them as independent and using Wegscheider's conditions to compute the remaining ones [63, 10] or by changing the parametrization so that in the new one the thermodynamic constraints are automatically observed [8, 64, 16].

2.2. Stochastic model with random parameters

Below we define DM with random parameters in a way typical of Bayesian statistics (see [6] Section 20 and Definition 17 of conditional distribution in Appendix A).

Definition 2. We say that the pair $M = (Y, P)$ consisting of a process Y and random vector P is DM with distribution of parameters μ_P and corresponding to chemical reaction network RN, if $P \sim \mu_P$, Y is a right-continuous nonexplosive process and $\mu_{DMCP}(RN(k), c)$ is conditional distribution of Y given $P = (c, k)$. Y is called the process and P the parameters of M .

One can construct DM with distribution of parameters μ_P and corresponding to a reaction network RN by setting, for some $P = (C, K) \sim \mu_P$ and independent of artificial noise variable R used by one of constructions of DMCP from Section 1.3 $c := C$ and $k := K$ at the beginning of this construction and then proceeding with it, given that such RN and c, k always admit DMCP. Using function h (1.15) given by the construction of DMCP the process of DM we just defined can be written as

$$Y = h(P, R). \quad (2.1)$$

The fact that Y conforms to definition of the process of DM is consequence of (1.16) and Theorem 18 in Appendix A. Analogously to what we did in case of process of DM we can define random parameters versions Y of other types of stochastic processes with constant parameters and provide their constructions in form of a function of independent parameters P and artificial noise R . Similarly as in Definition 2 of DM we consider pairs (Y, P) with the same distribution of P and conditional distribution of Y given P to be just different representations of the same model.

2.3. Parameters of conditional distribution

By observables of a process Y we mean its functions $g(Y)$ which are real-valued random variables or random vectors. An observable could be for instance the number of particles of certain species at some moment of time or its maximum number over some time period. In contrast to deterministic models with random parameters, in stochastic ones one cannot speak of a single value of the output given the parameters, but rather of its conditional distribution given the parameters and parameters of this distribution like conditional expectation. Conditional expectation of a random variable $Z \in L^1(\mathbb{P})$ (see Appendix A for definition of $L^p(\mathbb{P})$ for certain probability measure \mathbb{P} and properties of conditional expectation) given another variable X , denoted by $\mathbb{E}(Z|X)$, is formalization of the notion of the mean of Z given X and is a certain function of X . Let us now denote $L_n^p(\mathbb{P})$ or when \mathbb{P} is implicitly assumed shortly L_n^p , to be the space of random vectors $X = (X_i)_{i=1}^n$, such that $X_i \in L^p(\mathbb{P})$, for $i \in I_n$. For n bins given by numbers $(-\infty = a_1 < a_2 < \dots < a_{n+1} = \infty)$ histogram function hist is defined as

$$\text{hist}(x) := (\mathbb{1}_{[a_i, a_{i+1}]}(x))_{i=1}^n. \quad (2.2)$$

An example of vector-valued observable is a (single-sample) histogram $\text{hist}(Z)$ corresponding to a real-valued random variable Z . Note that $\text{hist}(Z) \in L_n^p$ for every p natural positive. For random vectors $Z = (Z_i)_{i=1}^n \in L_n^1(\mathbb{P})$ and X we define conditional expectation of Z given X as

$$\mathbb{E}(Z|X) = (\mathbb{E}(Z_i|X))_{i=1}^n. \quad (2.3)$$

Conditional histogram of Z given some random variable X is defined as $\mathbb{E}(\text{hist}(Z)|X)$ and mean histogram as $\mathbb{E}(\text{hist}(Z))$. For a vector $X = (X_1, \dots, X_N)$ and any $J \subset I_N$ let $X_J =$

$(X_i)_{i \in J}$. It is a well-known fact that for $Z \in L_n^1(\mathbb{P})$ for any n natural positive and $J \subset K \subset I_n$ we have the following iterated expectation property [15]

$$\mathbb{E}(\mathbb{E}(Z|X_K)|X_J) = \mathbb{E}(Z|X_J), \quad (2.4)$$

where by $\mathbb{E}(Z|X_\emptyset)$ we mean $\mathbb{E}(Z)$. For constructions of stochastic processes used in computer simulations, which are of form (2.1) observable of the process can also be written as a function of parameters P and the noise term R

$$f(P, R) := g(h(P, R)). \quad (2.5)$$

From Theorem 16 in Appendix 2.4 we receive that conditional expectation of such observable can be written in the following intuitive form

$$\tilde{f}(P) := \mathbb{E}(f(P, R)|P) = (\mathbb{E}(f(p, R)))_{p=P}. \quad (2.6)$$

2.4. Hilbert spaces

We now introduce some definitions and facts from Hilbert space theory, which are used in the following sections (see references [50] and [31] for proofs and more details). Hilbert space is a linear space H , for which there exists metric d induced by a norm $\|\cdot\|$, which is induced by certain scalar product (\cdot, \cdot)

$$d(x, y) := \|x - y\| := \sqrt{(x - y, x - y)}, \quad (2.7)$$

such that (H, d) is complete metric space. Examples of Hilbert spaces are $L^2(\mu)$ for different measures μ , with scalar product given by

$$(f, g) = \int f g \, d\mu. \quad (2.8)$$

For linear subspaces W_1, \dots, W_n of certain linear space their sum is denoted and defined as follows

$$\sum_{i=1}^n W_i := \left\{ \sum_{i=1}^n w_i : \forall i \in I_n \quad w_i \in W_i \right\}. \quad (2.9)$$

Definition 3. *Hilbert space H is direct sum of its linear subspaces H_1, \dots, H_n , which we denote*

$$H = \bigoplus_{i=1}^n H_i = H_1 \oplus \dots \oplus H_n \quad (2.10)$$

if the following conditions are fulfilled.

1. Subspaces H_1, \dots, H_n are closed.

2.

$$H = \sum_{i=1}^n H_i. \quad (2.11)$$

3. These subspaces are mutually orthogonal, that is for every $i, j \in I_n$, $i \neq j$ for every $v_i \in H_i$ and $v_j \in H_j$

$$(v_i, v_j) = 0. \quad (2.12)$$

It turns out that elements $v_i \in H_i$ for $i \in I_n$ such that

$$v = \sum_{i=1}^n v_i \quad (2.13)$$

are uniquely determined. Since for every $J \subset S_n$ the subspace

$$H_J = \sum_{i \in J} H_i \quad (2.14)$$

can be proved to be closed, thus it is Hilbert space for which we further have $H_J = \bigoplus_{i \in J} H_i$. For any partition $\{J \cup K\}$ of I_n it holds

$$H = H_J \oplus H_K. \quad (2.15)$$

We define direct product of n Hilbert spaces $(H_i)_{i=1}^n$ with respective scalar products $((\cdot, \cdot)_i)_{i=1}^n$ to be the the Cartesian product space $H_1 \times \dots \times H_n$ with scalar product defined as

$$(v, w) = \sum_{i=1}^n (v_i, w_i)_i. \quad (2.16)$$

It can easily be proved to be complete, thus it is Hilbert space. If M is any closed subspace of H then $M^\perp = \{v \in H : \forall w \in M \quad v \perp w\}$ is the unique subspace of H for which it holds

$$H = M \oplus M^\perp. \quad (2.17)$$

For every $v \in H$ the uniqueness of decomposition

$$v = v_M + v_{M^\perp}, \quad (2.18)$$

where $v_M \in M$ and $v_{M^\perp} \in M^\perp$, allows to define a linear function P_M from H onto M , such that $P_M(v) = v_M$. P_M is called orthogonal projection of H onto M . v_M is the unique element of M minimizing distance from v , that is

$$d(v, v_M) = \inf_{w \in M} d(v, w) \quad (2.19)$$

and it holds

$$d(v, v_M)^2 = \|v\|^2 - \|v_M\|^2. \quad (2.20)$$

2.5. Conditional expectation as orthogonal projection and generalizations of variance

$L^2(\mathbb{P})$ is Hilbert space with scalar product $(,)$ defined as

$$(X, Y) := \mathbb{E}(XY). \quad (2.21)$$

We denote the norm it induces $\|\cdot\|$ and the metric d . For some n natural positive let $<, >_n$ be any scalar product on \mathbb{R}^n . Let $(a_{ij})_{i,j \in I_n}$ be real numbers such that for every $x, y \in \mathbb{R}^n$ we have

$$< x, y >_n = \sum_{i,j \in I_n} a_{ij} x_i y_j. \quad (2.22)$$

For instance for the standard scalar product we have $a_{ij} = \delta_{ij}$, where δ_{ij} is Kronecker delta. We denote the norm induced by $<, >_n$ as $\|\cdot\|_n$ and the distance it induces d_n . We define Hilbert space on L_n^2 for any n natural positive by equipping it with scalar product $(,)_n$ defined for $X, Y \in L_n^2$ as

$$(X, Y)_n := \mathbb{E}(< X, Y >_n) = \sum_{i,j \in I_n} a_{ij} (X_i, Y_j). \quad (2.23)$$

We denote the norm it induces by $\|\cdot\|_n$ and the distance d_n . We say that 2 norms $|\cdot|_1, |\cdot|_2$ on the linear space A are equivalent, if there exist α and β real positive such that

$$\forall x \in A \quad |x|_1 \leq \alpha |x|_2 \leq \beta |x|_1. \quad (2.24)$$

The completeness of L_n^2 with norm induced by any above defined scalar product $(\cdot, \cdot)_n$ is a consequence of the fact that for $\langle \cdot, \cdot \rangle_n$ equal to standard scalar product the defined space becomes an n -fold direct sum of L^2 , which is complete (see Section 2.4) and the well-known fact that all norms in finite dimensional spaces like \mathbb{R}^n are equivalent and from (2.23) so are different $\|\cdot\|_n$.

Let us denote $L_{n,X}^2$ (L_X^2) to be the subspace of L_n^2 ($L^2(\mathbb{P})$) consisting of all its elements being certain functions of random variable X . This is a closed subspace.

Theorem 4. *If $Z \in (L_n^2)$ and X is a random variable, then $\mathbb{E}(Z|X)$ is orthogonal projection of Z onto $L_{n,X}^2$.*

Proof. We have $\mathbb{E}(Z|X) \in L_{n,X}^2$. Furthermore, for any $f(X) = (f_j(X))_{j=1}^n \in L_{n,X}^2$ we have

$$(Z - \mathbb{E}(Z|X), f(X))_n = \sum_{i,j \in I_n} a_{ij} (Z_i - \mathbb{E}(Z_i|X), f_j(X)) = 0, \quad (2.25)$$

since for all $i \in I_n$ it holds $Z_i - \mathbb{E}(Z_i|X) \in (L_X^2)^\perp$, because $\mathbb{E}(\cdot|X)$ is orthogonal projection from $L^2(\mathbb{P})$ onto L_X^2 (see [15], Sec. 4.1 Theorem 1.4). We thus have $Z - \mathbb{E}(Z|X) \in (L_{n,X}^2)^\perp$. \square

As orthogonal projection, $\mathbb{E}(Z|X)$ is the best approximation of Z among all functions of X in L_n^2 and the error of this approximation fulfills

$$d_n(Z, \mathbb{E}(Z|X))^2 = \|Z\|_n^2 - \|\mathbb{E}(Z|X)\|_n^2. \quad (2.26)$$

For random variable $Z \in L^2(\mathbb{P})$ by its variance we mean

$$\text{Var}(Z) = \mathbb{E}(Z - \mathbb{E}Z)^2 = \mathbb{E}(Z^2) - \mathbb{E}^2(Z), \quad (2.27)$$

while by conditional variance of Z given X

$$\text{Var}(\mathbb{E}(Z|X)) := \mathbb{E}(Z^2|X) - \mathbb{E}^2(Z|X) = \mathbb{E}((Z - \mathbb{E}(Z|X))^2|X). \quad (2.28)$$

We generalize variance to random vectors $Z \in L_n^2$ as follows

$$\text{Var}(Z) := d_n(Z, \mathbb{E}(Z))^2 = \|Z\|_n^2 - \|\mathbb{E}(Z)\|_n^2 \quad (2.29)$$

and conditional variance of Z given X as

$$\text{Var}(Z|X) := \mathbb{E}(\text{dist}_n(Z, \mathbb{E}(Z|X))^2|X). \quad (2.30)$$

Using iterated expectation property (2.4) we rewrite (2.26) to receive generalized version of a well-known formula

$$\text{Var}(Z) = \mathbb{E}(\text{Var}(Z|X)) + \text{Var}(\mathbb{E}(Z|X)). \quad (2.31)$$

One can further generalize variance and conditional variance to the case of random vectors by using metrics D_n on \mathbb{R}^n , which are not induced by scalar products and defining variance as $\mathbb{E}(D_n(Z, \mathbb{E}(Z))^2)$ and conditional variance as in (2.30) with dist_n replaced with D_n . For instance Degasperi et. al. ([13] and e-mail communication with Mr Degasperi) apply k -dimensional Manhattan distance for some k natural

$$DM_k(X, Y) = \sum_{i=1}^k |X_i - Y_i| \quad (2.32)$$

to compute such defined variances for conditional histogram $Z = \mathbb{E}(\text{hist}(f(P, R))|P)$ of some observable $f(P, R)$ of the process of DM and variance of $\mathbb{E}(Z|X)$ for $X = P_J$, where P_J is certain subvector of P . Such variances are called main-sensitivity indices of Z with

respect to P and P_J respectively and we discuss them in more detail in further Sections. Unfortunately, for variances and conditional variances defined using metric (2.32), formula (2.31), which is crucial for some applications of variance-based sensitivity indices, in general does not hold. For instance let us consider histogram function h with bins given by ($a_1 = -\infty$, $a_4 = \infty$ and $a_{i+1} = -3 + i * 2$ for $i \in I_2$) and two independent random variables ϵ_1, ϵ_2 with distribution $\mathbb{P}(\epsilon_i = 1) = \mathbb{P}(\epsilon_i = -1) = \frac{1}{2}$, for $i \in I_2$. For $Z = \epsilon_1 + \epsilon_2$ we have $\text{Var}(h(Z)) = \frac{13}{8}$, $\text{Var}(\mathbb{E}(h(Z)|\epsilon_1)) = \frac{1}{4}$ and

$$\mathbb{E}(D_3(h(Z), \mathbb{E}(h(Z)|\epsilon_1)^2) = 1, \quad (2.33)$$

thus the counterpart of expression (2.31) does not hold.

Chapter 3

Variance-based sensitivity analysis

3.1. ANOVA decomposition

In this whole Section $X = (X_1, \dots, X_N)$ is a random vector with independent coordinates, f is a function such that $f(X) = (f_i(X))_{i=1}^n \in L_n^2$ for some n natural positive. We denote $I := I_n$. For $J \subset I$ vector X_J is defined as in Section 2.3. For $J \neq \emptyset$ $L_{X_J}^2$ is defined as in Section 2.5 and $L_{X_\emptyset}^2$ denotes the set of all real constants. We further denote $X_{\sim i}$ to be the sub vector of X with all its coordinates except for the i -th. For each $J \subset I$ let us denote $L_{n,J}^2$ to be the subspace of L_{n,X_J}^2 consisting of variables $Z = f(X_J)$ such that for every $i \in J$ we have

$$\mathbb{E}(Z|X_{\sim i}) = \int f(X_{J \setminus \{i\}}, x_i) \mu_i(dx_i) = 0, \quad (3.1)$$

where expression in the middle is a convenient notation for integrating only the i -th variable over its distribution and the first equality is a consequence of Theorem 16 from Appendix A. Note that $L_{n,\emptyset}^2$ denotes the subspace of constant vectors. From (3.1) and iterated expectation property (2.4) it follows that elements $Z_J \in L_{n,J}^2$ for $J \neq \emptyset$ fulfill

$$\mathbb{E}(Z_J) = 0. \quad (3.2)$$

We now introduce generalization of well-known ANOVA decomposition to the case of elements of $L_{n,X}^2$. To our knowledge ANOVA decomposition for real-valued variables appeared for the first time in [17]. See [32] and [2] for different formulations and alternative proofs of this decomposition for the special case of real-valued functions and for reviews of its history.

Theorem 5. *For Hilbert space $L_{n,X}^2$ with certain scalar product $(\cdot, \cdot)_n$ as discussed in Section 2.5, we have*

$$L_{n,X}^2 = \bigoplus_{J \subset I} L_{n,J}^2. \quad (3.3)$$

Proof. For every $J \subset I$ set $L_{n,J}^2$ is closed in $L_{n,X}^2$, since it is intersection of closed set L_{n,X_J}^2 and $\mathbb{E}^{-1}(\cdot|X_{\sim i})(0)$ for $i \in J$, which are closed due to conditional expectations being continuous as any orthogonal projections. We need to prove that for every $f(X) \in L_{n,X}^2$ there exist $f_J(X_J) \in L_{n,J}^2$ for $J \subset I$, such that we have

$$f(X) = \sum_{J \subset I} f_J(X_J). \quad (3.4)$$

Notice that for $K, J \subset I$ such that $\exists i \in K \cap (I \setminus J)$ from $f_K(X_K) \in L_{n,K}^2$ it follows

$$\mathbb{E}(f_K(X_K)|X_J) = \mathbb{E}\left(\int f_K(X_{K \setminus \{i\}}, x_i) \mu_i(dx_i)|X_J\right) = 0. \quad (3.5)$$

Applying conditional expectation $\mathbb{E}(\cdot|X_J)$ to both sides of (3.4) for $J \subset I$ and using (3.5) we receive set of formulas

$$\{\mathbb{E}(f(X)|X_J) = \sum_{K \subset J} f_K(X_K)\}_{J \in I}, \quad (3.6)$$

which uniquely determine every $f_J(X_J)$ on the right hand side (rhs) of (3.4) (full proof would follow by induction over $|J|$ - the size of J). The fact that such defined $f_K(X_K)$ are in respective spaces $L_{K,n}^2$ follows by induction. For $f_\emptyset = \mathbb{E}(f(X))$ it is obvious. Let us assume for certain $k < n$ it holds for all $\{J \subset I : |J| \leq k\}$. We prove it for $\{J : |J| = k+1\}$ as follows. For $i \in J$ from formulas (3.6) we have

$$\mathbb{E}(f_J(X_J)|X_{\sim i}) = \mathbb{E}(f(X)|X_{J \setminus \{i\}}) - \sum_{K \subset (J \setminus \{i\})} f_K(X_K), \quad (3.7)$$

since

$$\mathbb{E}\left(\int f(X_{J \setminus \{i\}}, x_i) \mu_i(dx_i) | X_J\right) = \mathbb{E}(f(X)|X_{J \setminus \{i\}}) \quad (3.8)$$

and by inductive hypothesis for $K \subsetneq J$, $i \in K$ $f_K(X_K)$ become 0 when applying to them $\mathbb{E}(\cdot|X_{\sim i})$, while $f_K(X_K)$ for $i \notin K$ remain unchanged. From (3.6) the rhs of (3.7) is equal to zero vector. Finally, for $J, K \subset I$, $J \neq K$ we need to prove that $f_J(X_J)$ and $f_K(X_K)$ are orthogonal. Without loss of generality assuming that there exists certain $i \in J \setminus K$, for every $l, m \in I$ we have

$$\mathbb{E}(f_{J,l}(X_J) f_{K,m}(X_K)) = \mathbb{E}\left(\int f_{J,l}(X_{J \setminus \{i\}}, x_i) \mu_i(dx_i) f_{K,m}(X_K)\right) = 0, \quad (3.9)$$

so from expression (2.23) we receive $(f_J(X_J), f_K(X_K))_n = 0$. \square

Vector $(f_J(X_J))_{J \subset I}$ as in the above theorem is called ANOVA decomposition of $f(X)$. Denoting for $J \subset I$

$$V_J := \text{Var}(f_J(X_J)) \quad (3.10)$$

and using (3.4) and orthogonality of elements of ANOVA decomposition we get

$$\text{Var}(f(X)) = \sum_{K \subset I} V_K. \quad (3.11)$$

We call $(V_K)_{K \subset I}$ the ANOVA decomposition of variance of $f(X)$. For convenience instead of writing $V_{\{i,j,\dots,k\}}$ we write simply $V_{i,j,\dots,k}$. For a family \mathcal{S} of subsets of I such that

$$\forall A \in \mathcal{S} \quad \forall B \subset A \quad B \in \mathcal{S} \quad (3.12)$$

we have

$$\sum_{J \in \mathcal{S}} L_{n,X_J}^2 = \bigoplus_{J \in \mathcal{S}} L_{n,J}^2. \quad (3.13)$$

From expressions (2.17) and (2.19) from Section 2.4 it thus follows that $\sum_{J \in \mathcal{S}} f_J$ is the best approximation of $f(X)$ among linear combinations of functions of one of sub vector from the set $\{X_J\}_{J \in \mathcal{S}}$. From (3.11) and (2.20) error of this approximation is equal to

$$\sum_{J \subset I, J \notin \mathcal{S}} V_J. \quad (3.14)$$

For fixed $J \subset I$ subtracting expression (3.14) for $\mathcal{S} = \{K : K \subsetneq J\}$ from this expression for \mathcal{S} equal to all subsets of J , we receive V_J . Thus V_J can be interpreted as the difference of errors of the best approximation of $f(X)$ using linear combinations of functions of proper sub vectors of X_J and of the whole vector X_J . This is to our knowledge new interpretation of V_J , which has been called interaction index between variables with indices in J in the literature [53].

3.2. Variance-based sensitivity indices

For some m natural positive let $Z \in L_m^2$ and $X = (X_i)_{i=1}^n$ be a random vector. We denote $I = I_n$. X_J for some $J \subset I$ is defined as in the previous Section. We assume that $\text{Var}(Z) = D > 0$. One useful sensitivity index describing dependence of Z on X_J is variance of conditional expectation of Z given X_J , which is known as the main sensitivity index of Z with respect to X_J [2]

$$V_{X_J} := \text{Var}(\mathbb{E}(Z|X_J)). \quad (3.15)$$

We call its normalized version

$$S_{X_J} = \frac{V_{X_J}}{D} \quad (3.16)$$

Sobol's main sensitivity index [53]. From (2.31) $D - V_{X_J}$ is equal to the error of the best approximation of Z in L_{m,X_J}^2 , in particular when $S_{X_J} = 1$ we receive that Z is a function of X_J . Let us now assume that $Z = f(X)$ for certain function f and random vector $X = (X_i)_{i=1}^n$. Denoting $\sim J := I \setminus J$, we define the total sensitivity index $f(X)$ with respect to X_J [53]

$$V_{X_J}^{tot} := D - V_{X_{\sim J}}, \quad (3.17)$$

where $\sim J = I \setminus J$. Its normalized version, is called Sobol's total sensitivity index

$$S_{X_J}^{tot} = \frac{V_{X_J}^{tot}}{D}. \quad (3.18)$$

$V_{X_J}^{tot}$ is equal to the error of the best approximation of $f(X)$ among functions of $X_{\sim J}$ from L_m^2 . In particular

$$S_{X_J}^{tot} = 0 \Leftrightarrow f(X) = \mathbb{E}(f(X)|X_{\sim J}). \quad (3.19)$$

Let us now assume that X_J and $X_{\sim J}$ are independent. Since $\mathbb{E}(f(X)|X_{\sim J})$ is function of $X_{\sim J}$ the rhs of (3.19) implies that $f(X)$ is independent of X_J . By treating $f(X)$ as a function of two arguments X_J and $X_{\sim J}$ we get its variance decomposition sum analogical to (3.11)

$$D = V_{X_J} + V_{X_J, X_{\sim J}} + V_{X_{\sim J}}. \quad (3.20)$$

where $V_{X_J, X_{\sim J}}$ is the interaction index of X_J and $X_{\sim J}$. From (3.17) we get that

$$V_{X_J}^{tot} = V_{X_J} + V_{X_J, X_{\sim J}}. \quad (3.21)$$

If all coordinates of X are independent, using (3.11) we rewrite (3.17) as

$$V_{X_J}^{tot} = \sum_{K \subset I: K \cap J \neq \emptyset} V_K, \quad (3.22)$$

which is the sum of all interaction terms involving indices from J . Equations (3.21) and (3.22) provide some intuition for the name total effect of X_J on $f(X)$ for $V_{X_J}^{tot}$ and prove that

$$0 \leq S_{X_J} \leq S_{X_J}^{tot} \leq 1. \quad (3.23)$$

For X_J and $X_{\sim J}$ not independent neither inequalities (3.23) nor the fact that $S_{X_J}^{tot} = 0$ implies independence of X_J and Z are true, for instance for $X_J = X_{\sim J}$ we get $S_{X_J} = 1$, $S_{X_J}^{tot} = 0$ and $f(X)$ is not independent of X_J .

3.3. Sensitivity indices for observables of DM

Let us consider certain observable $g(Y) \in L_n^2$ of a process Y of a DM with parameters P . We define main sensitivity index of $g(Y)$ given some sub vector of P_J as in the previous Section. Its value V_{P_J} is determined by the distribution of $\mathbb{E}(g(Y)|P_J)$, which is determined by distribution of P and conditional distribution of Y given P , and hence by Definition 2 of DM (see Appendix A). Introducing a representation $f(P, R)$ (2.5) of the observable related to a certain construction of the process of this DM, we can consider some further sensitivity indices. For instance

$$V_R^{tot} := D - V_P, \quad (3.24)$$

whose value, by inspection of rhs of (3.24) is also determined by definition of DM. However, the values of indices of $f(P, R)$ like $V_R = \text{Var}(\mathbb{E}(f(P, R)|R))$ or $V_{P_J}^{tot} = D - V_{(P_{\sim J}, R)}$ are not determined by Definition 2 and can be different for different constructions of DM used to define $f(P, R)$. Let us consider the mean observable $g(Y)$ given P

$$\tilde{f}(P) := \mathbb{E}(g(Y)|P). \quad (3.25)$$

Thanks to iterated expectation property (2.4) we have $\mathbb{E}(\tilde{f}(P)|P_J) = \mathbb{E}(g(Y)|P_J)$ and therefore the main sensitivity indices of $\tilde{f}(P)$ and $g(Y)$ with respect to P_J coincide

$$\tilde{V}_{P_J} := \text{Var}(\mathbb{E}(\tilde{f}(P)|P_J)) = V_{P_J}, \quad (3.26)$$

while for total sensitivity indices we have

$$\tilde{V}_{P_J}^{tot} := \tilde{D} - \tilde{V}_{P_{\sim J}} = V_P - V_{P_{\sim J}}. \quad (3.27)$$

Defining $\tilde{D} := \text{Var}(\tilde{f}(P)) = \tilde{V}_P$ we also have following expressions for Sobol's sensitivity indices of $\tilde{f}(P)$

$$\tilde{S}_{P_J} := \frac{\tilde{V}_{P_J}}{\tilde{D}} = \frac{V_{P_J}}{V_P}, \quad (3.28)$$

$$\tilde{S}_{P_J}^{tot} := \frac{\tilde{V}_{P_J}^{tot}}{\tilde{D}} = \frac{V_P - V_{P_{\sim J}}}{V_P}. \quad (3.29)$$

3.4. Measures of dispersion for uncertain models

From (2.31) average conditional variance of $Z \in L_n^2$ given some variable X can be expressed using main sensitivity index as follows

$$\mathbb{E}(\text{Var}(Z|X)) = D - V_X. \quad (3.30)$$

Note that the last expression is equal to V_R^{tot} for an observable $Z = f(P, R)$ corresponding to certain construction of DM and $X = P$. Since variance is a measure of dispersion of distribution of model output with known parameters, average conditional variance given the epistemic parameters could be used to measure and compare dispersions of models with uncertain parameters. For chemical models with constant parameters p also other measures of dispersion of process observables Z_p satisfying $\mathbb{E}(Z_p) > 0$ have been used, like coefficient of variation

$$CV = \frac{\sqrt{\text{Var}(Z_p)}}{\mathbb{E}(Z_p)}, \quad (3.31)$$

which is a dimensionless quantity, or Fano factor [19, 58]

$$FF = \frac{\text{Var}(Z_p)}{\mathbb{E}(Z_p)}. \quad (3.32)$$

For variables with Poisson distribution variance is equal to mean and hence FF reveals whether Z_p has greater variance than a Poisson variable with the same mean. For outputs Z of models with uncertain parameters one could take an average of a conditional FF $\mathbb{E} \frac{\sqrt{\text{Var}(Z|X)}}{\mathbb{E} Z|X}$, and similarly for CV. Instead we propose the following generalizations of conditional variance GCV and Fano factor GFF to the random parameters case

$$\text{GCV} = \frac{\sqrt{\mathbb{E} \text{Var}(Z|X)}}{\mathbb{E}(Z)} \quad (3.33)$$

and

$$\text{GFF} = \frac{\mathbb{E}(\text{Var}(Z|X))}{\mathbb{E}(Z)}, \quad (3.34)$$

since they can be expressed using variance based sensitivity indices as in (3.30) and hence are amenable for computation using our methods. We call them generalizations, since they coincide with definitions for models with constant parameters when the distribution of epistemic parameters is one-point.

3.5. Average variance reduction

We assume Z is some model output, like an observable $g(Y)$ of process of DM or its mean, conditional histogram or some conditional moment given the parameters. For random vector X denoting model parameters we define its subvector X_J as usual. We rewrite expression (2.31) as follows

$$S_{X_J} = \frac{\mathbb{E}(D - \text{Var}(Z|X_J))}{D}. \quad (3.35)$$

The rhs of (3.35) is the normalized average difference of variance of Z and its conditional variance given X_J . Thus if X_J are epistemic parameters, S_{X_J} tells by what fraction on average the variance of the output is reduced if we get to know their exact values. Let us assume that we can conduct an experiment measuring completely precisely one epistemic parameter, which is of course an idealisation. If we want to achieve on average the highest reduction of the variance of the output, which can also be thought of as maximal reduction of the uncertainty or improvement of the precision of model predictions, we should measure the parameter with highest main sensitivity index V_{X_i} . This approach to using variance-based sensitivity indices is known as factor prioritization setting [52].

3.6. Parameter fixing

Let us consider a function $f(X) \in L_m^2$ of a random vector X , whose sub vectors X_J and $X_{\sim J}$ are independent. As shown for the case of $m = 1$ in [55] $V_{X_J}^{tot}$ is related to the average error made when fixing variable X_J , in the sense we describe and prove for arbitrary m in this Section. Using certain d_m and $dist_m$ as in Section 2.5 we define the square error of approximation of $f(X)$ when fixing X_J to value $z \in \mathbb{R}^m$ as follows

$$\Delta(z) = (d_m(f(z, X_{\sim J}), f(X)))^2 = \mathbb{E}((\text{dist}_m(f(z, X_{\sim J}), f(X)))^2). \quad (3.36)$$

We further need the following Theorem.

Theorem 6. *For $X = (X_1, X_2)$, $Y_2 \sim X_2$ and independent of X and $g(X), h(X) \in L^2(\mathbb{P})$ it holds*

$$\mathbb{E}(g(X)h(X_1, Y_2)) = \mathbb{E}(\mathbb{E}(g(X)|X_1)\mathbb{E}(h(X)|X_1)). \quad (3.37)$$

In particular if $g(X) = h(X)$ we receive a well-known fact [51] that

$$\mathbb{E}(g(X)g(X_1, Y_2)) = \mathbb{E}((\mathbb{E}(g(X)|X_1))^2) \quad (3.38)$$

and the fact that

$$\text{Cov}(g(X), g(X_1, Y_2)) = \text{Var}(\mathbb{E}(g(X)|X_1)). \quad (3.39)$$

Proof.

$$\begin{aligned} \mathbb{E}(g(X)h(X_1, Y_2)) &= \mathbb{E}(\mathbb{E}(g(X)h(X_1, Y_2)|X_1)) \\ &= \mathbb{E}((\mathbb{E}(g(x_1, X_2)h(x_1, Y_2))_{x_1=X_1}) \\ &= \mathbb{E}((\mathbb{E}(g(x_1, X_2)))_{x_1=X_1}(\mathbb{E}(h(x_1, Y_2)))_{x_1=X_1}) \\ &= \mathbb{E}(\mathbb{E}(g(X)|X_1)\mathbb{E}(h(X)|X_1)), \end{aligned} \quad (3.40)$$

where in first equality we used iterated expectation property, in the second and last Theorem 16 and in the third independence of X_2 and Y_2 . \square

Let $Y_J \sim X_J$ and be independent of X . From the above Theorem it follows that

$$\begin{aligned} (f(X), f(Y_J, X_{\sim J}))_m &= \sum_{i,j \in I_m} a_{ij}(f_i(X), f_j(Y_J, X_{\sim J})) \\ &= \sum_{i,j \in I_m} a_{ij}(\mathbb{E}(f_i(X)|X_{\sim J}), \mathbb{E}(f_j(X)|X_{\sim J})) \\ &= \|\mathbb{E}(f(X)|X_{\sim J})\|_m^2. \end{aligned} \quad (3.41)$$

Thus if X_J is set randomly according to its distribution the mean square error of approximation of $f(X)$ is

$$\begin{aligned} \mathbb{E}(\Delta(Y_J)) &= \mathbb{E}(\text{dist}_m(f(Y_J, X_{\sim J}), f(X))^2) \\ &= \|f(X)\|_m^2 + \|f(Y_J, X_{\sim J})\|_m^2 - 2(f(X), f(Y_J, X_{\sim J}))_m \\ &= 2(D - V_{X_{\sim J}}) = 2V_{X_J}^{tot}. \end{aligned}$$

The normalized mean square error $\frac{\mathbb{E}(\Delta(Y_J))}{D}$ of the approximation mentioned is thus equal to $2S_{X_J}^{tot}$. When $V_{X_J}^{tot} = 0$ then for μ_{X_J} almost every (a.e) y_J , for μ_X a. e. $x = (x_J, x_{\sim J})$ we have that $f(x) = f(y_J, x_{\sim J})$. Therefore, if we need to evaluate many independent copies of $f(X)$, for instance in a Monte Carlo simulation we can fix X_J to some random value y_J at the beginning and evaluate independent copies of $f(y_J, X_{\sim J})$ instead. With probability 1 we get the same result, but at smaller cost, as there is no need to generate many independent copies of X_J . The cost of generation of random parameters of chemical models is usually completely insignificant in comparison to the cost of function evaluation, but if X_J represents component of artificial noise R of some stochastic model like DM the cost of its generation forms a noticeable fraction of the overall simulation cost [37]. The computation of $S_{X_J}^{tot}$ for the purpose of identifying and fixing insignificant parameters is known as factor fixing setting [52].

One is often interested in fixing X_J not to random value, but to a certain one, possibly even lying outside the support of the distribution μ_{X_J} , but leading to significant reduction of computational cost of function evaluation. For instance if X represents kinetic rates of chemical reaction network, we may be interested in fixing some of them to 0 or 1, which can lead to model reduction like removal of certain reactions [14]. Fixing parameters i with small values of $S_{X_i}^{tot}$ or even S_{X_i} to certain value in order to simplify the model can sometimes be useful heuristic leading to models retaining small approximation error from initial model or experimental data. For instance in [10] the sensitivity of error of approximation of experimental data by the model with respect to kinetic parameters was computed for different models describing the hydrogenation process of avermectin to ivermectin. It turned out that a simple model, which could be created from more complex ones by removal of reactions whose propensities had kinetic parameters with low values of main and total Sobol's indices retained good fitting capability to experimental data representing different values of model parameters.

Chapter 4

Estimation methods

4.1. Statistical models

Statistical model is a triplet $(B, \mathcal{B}, \mathcal{P})$, where $\mathcal{S} = (B, \mathcal{B})$ is a measurable space and \mathcal{P} is a family of admissible distributions. Functions from \mathcal{S} are called statistics. For a given $\mu \in \mathcal{P}$ random variable $X \sim \mu$ and its functions are called observables. For fixed $\mu \in \mathcal{P}$ ϕ can be treated as a random variable on probability space (\mathcal{S}, μ) and we denote its expectation as

$$\mathbb{E}_\mu \phi := \int \phi d\mu. \quad (4.1)$$

Let us consider certain real-valued function G on \mathcal{P} , which is called estimand. For instance if $\mathcal{S} = (\mathbb{R}, \mathcal{B}(\mathbb{R}))$ the estimand could be the first moment of μ

$$G(\mu) = \int x \mu(dx), \quad (4.2)$$

assuming it exists for every $\mu \in \mathcal{P}$. Statistic ϕ is called estimator of G , if for every $\mu \in \mathcal{P}$, for any observable $X \sim \mu$, one may use $\phi(X)$ to approximate $G(\mu)$. As a measure of error of this approximation for given $\mu \in \mathcal{P}$ one can use mean square error

$$\mathbb{E}_\mu(\phi - G(\mu))^2. \quad (4.3)$$

Value $\phi(X(\omega))$ corresponding to some random event ω is called estimate of $G(\mu)$. Statistic ϕ is called unbiased estimator of G , if for every $\mu \in \mathcal{P}$, we have

$$\mathbb{E}_\mu(\phi) = G(\mu). \quad (4.4)$$

For any statistic its variance given $\mu \in \mathcal{P}$ is defined as

$$\text{Var}_\mu(\phi) := \mathbb{E}_\mu(\phi - \mathbb{E}_\mu(\phi))^2. \quad (4.5)$$

Thanks to (4.4), for an unbiased estimator it is equal to its mean square error (4.3) in approximating $G(\mu)$. We further use following unbiased estimators defined on $\mathcal{S} = (\mathbb{R}^n, \mathcal{B}(\mathbb{R}^n))$ for some n natural positive and and with \mathcal{P} containing n -fold product measures μ^n , for which their estimands exist. Estimator of first moment of μ

$$\phi_{ave}(x) := \frac{1}{n} \sum_{i=1}^n x_i, \quad (4.6)$$

of variance of any variable with distribution μ for $n \geq 2$

$$\phi_{var}(x) := \frac{1}{n-1} \sum_{i=1}^n (x_i - \phi_{ave}(x))^2 \quad (4.7)$$

and of variance of estimator ϕ_{ave} given μ for $n \geq 2$

$$\phi_{avevar}(x) := \frac{\phi_{var}(x)}{n}. \quad (4.8)$$

4.2. Monte Carlo method

Let us assume that $\phi \in L^2(\mu)$, for some probabilistic measure μ . Monte Carlo (MC) method is a procedure of computing estimates of integrals of form

$$\lambda = \int \phi d\mu. \quad (4.9)$$

Note that for statistical model containing only one admissible distribution μ ϕ is an unbiased estimator of estimand λ . In such situation we say that ϕ is unbiased estimator of λ with respect to μ . For independent random variables $(X_i)_{i=1}^n$, $X_i \sim \mu$ generated for instance using random number generator, in each step of MC procedure one computes a value of observable $W_i = \phi(X_i)$. Thus we call ϕ single-step (MC) estimator. For $W = (W_i)_{i=1}^n$ and ϕ_{ave} as in the previous Section as final MC estimate of λ one uses the computed value of observable

$$\bar{W} := \phi_{ave}(W). \quad (4.10)$$

Function defined as

$$\phi_{fin}(x) = \phi_{ave}((\phi(x_i))_{i=1}^n) \quad (4.11)$$

is an unbiased estimator of λ with respect to μ^n and we call it final (MC) estimator. Let us denote the variance of single-step estimator as $\text{Var}_s := \text{Var}_{\mu}(\phi) = \text{Var}(W_i)$ for any $i \in I_n$ and the variance of final estimator as $\text{Var}_a := \text{Var}_{\mu^n}(\phi_{ave}((\phi_i)_{i=1}^n)) = \text{Var}(\bar{W})$. It holds

$$\text{Var}_a = \frac{\text{Var}_s}{n}. \quad (4.12)$$

As estimates of Var_a one uses the values of

$$\widehat{\text{Var}}_a(W) := \phi_{avevar}(W) \quad (4.13)$$

and as estimates of standard deviation σ_a of \bar{W} the values of

$$\widehat{\sigma}_a(W) := \sqrt{\phi_{avevar}(W)}. \quad (4.14)$$

From central limit theorem [5], for large n \bar{W} should have approximately normal distribution. In particular $P(|\bar{W} - \lambda| < k\sigma_a)$ is then approximately equal to 68% for $k = 1$ and 95% for $k = 2$. We further report results of MC procedure using computed value of $\bar{W} \pm \widehat{\sigma}_a(W)$.

If we want to go with variance Var_a below threshold α for given Var_s , we should use smallest number n of MC steps, such that

$$\text{Var}_a = \frac{\text{Var}_s}{n} < \alpha. \quad (4.15)$$

We have

$$n \approx_{\epsilon} \frac{\text{Var}_s}{\alpha}, \quad (4.16)$$

by which we mean that it holds

$$\frac{n - \frac{\text{Var}_s}{\alpha}}{n} \leq \epsilon, \quad (4.17)$$

for some ϵ , which can be arbitrarily small for sufficiently small α (large n). If most of the time of MC procedure is taken by computation of W and computation of W_i in a single step lasts on average τ_s , then the whole procedure lasts on average about

$$n\tau_s \approx_{\epsilon} \frac{\tau_s \text{Var}_s}{\alpha}. \quad (4.18)$$

Let us define Monte Carlo step inefficiency constant as follows

$$c = \tau_s \text{Var}_s. \quad (4.19)$$

Let us assume that the same number λ can be estimated in MC procedures using different functions $\phi_i \in L^2(\mu_i)$, having different values of respective mean duration times $\tau_{s,i}$ of single step and variances of single step estimators $\text{Var}_{s,i}$ for i in some set A . When our goal is to minimize the average computation time needed to go below given error α and ϵ in the counterpart of equality (4.2) for each function ϕ_i is negligibly small, then from (4.18) we should choose i with minimum value of respective inefficiency constant c_i . Let us assume that for some n_i and τ_i for $i \in I_2$ denoting the number of steps and average duration of each step for two different Monte Carlo procedures respectively, we have approximate identity

$$n_1\tau_1 \approx_\delta n_2\tau_2. \quad (4.20)$$

The ratio of variances of final MC estimators $\text{Var}_{a,j}$ of these procedures is then approximately the same as the ratio of their respective inefficiency constants c_j)

$$\frac{\text{Var}_{a,1}}{\text{Var}_{a,2}} = \frac{\text{Var}_{s,1} n_2}{\text{Var}_{s,2} n_1} \approx_\delta \frac{c_1}{c_2}, \quad (4.21)$$

where $\text{Var}_{s,i}$ for $i \in I_2$ are the variances of their respective single-step estimators.

4.3. Schemes for estimation of sensitivity indices

For a given N natural positive let \mathcal{R}_N be the set of all pairs (f, μ) of product probability distributions $\mu = \mu_1 \times \dots \times \mu_N$ and measurable functions f , such that μ and f are defined on the same product of measurable spaces.

Definition 7. For a given N natural positive, by (generalized) estimand of order N we mean a real-valued function G on some subset \mathcal{R}_G of \mathcal{R}_N .

As an example of such generalized estimand of order 2 we define total sensitivity index V_1^{tot} of functions of two arguments with respect to the first argument by demanding that $\mathcal{R}_{V_1^{tot}} = \{(f, \mu) \in \mathcal{R}_2 : f \in L^2(\mu), \}$ and for any $(f, \mu) \in \mathcal{R}_{V_1^{tot}}$ and any $(X_1, X_2) \sim \mu$

$$V_1^{tot}(f)(\mu) := \mathbb{E}(f(X)^2) - \mathbb{E}(\mathbb{E}^2(f(X)|X_2)). \quad (4.22)$$

For product distribution $\mu = \mu_1 \times \dots \times \mu_N$ and $v = (v_i)_{i=1}^N$ we define

$$\mu^v = \mu_1^{v_1} \times \dots \times \mu_N^{v_N}. \quad (4.23)$$

Definition 8. A (generalized) unbiased estimator ϕ of estimand G of order N on \mathcal{R}_G with (vector of) dimensions of arguments $v = (v_1, \dots, v_N)$ is a function on the set $\{f : (f, \mu) \in \mathcal{R}_G\}$, such that for any $(f, \mu) \in \mathcal{R}_G$ $\phi(f)$ is unbiased estimator of $G(f, \mu)$ with respect to μ^v . In other words, if $\mu = \mu_1 \times \dots \times \mu_N$, then for any random vector $\tilde{X} = ((\tilde{X}_{i,j})_{i=1}^{v_j})_{j=1}^N$, whose elements are mutually independent and fulfill $\tilde{X}_{i,j} \sim \mu_j$, we have

$$\mathbb{E}(\phi(f)(\tilde{X})) = G(f, \mu). \quad (4.24)$$

Using notations from Definition 8, for $\phi(f) \in L^2(\mu)$ we denote

$$\text{Var}_{f,\mu}(\phi) := \text{Var}_{\mu^v}(\phi(f)) = \text{Var}(\phi(f)(\tilde{X})). \quad (4.25)$$

For any sets B_1, \dots, B_N and

$$B = B_1 \times \dots \times B_N \quad (4.26)$$

we denote

$$B^v = B_1^{v_1} \times \dots \times B_N^{v_N}. \quad (4.27)$$

We also denote

$$I_v := I_{v_1} \times \dots \times I_{v_N}. \quad (4.28)$$

For a point $\tilde{x} = ((\tilde{x}_{i,j})_{j=1}^{v_i})_{i=1}^N \in B^v$ and $j = (j_i)_{i=1}^N \in I_v$ we denote

$$\tilde{x}_j := (\tilde{x}_{i,j_i})_{i=1}^N. \quad (4.29)$$

and for any $i \in I_N$

$$\tilde{x}_i = (\tilde{x}_{i,l})_{l=1}^{v_i}. \quad (4.30)$$

For any $j \in I_v$ we denote by g_j a function on the set of all real-valued functions f on any product sets B as in (4.26), such that

$$g_j(f) : B^v \mapsto \mathbb{R} : g_j(f)(\tilde{x}) = f(\tilde{x}_j). \quad (4.31)$$

We also denote, for any finite subset $A \subset I_v$

$$g_A := (g_j)_{j \in A}. \quad (4.32)$$

We define

$$(A)_i := \{j_i : j \in A\}, \quad (4.33)$$

$$n_{A,i} = \max\{k : k \in (A)_i\}, \quad (4.34)$$

and $n_A = (n_{A,i})_{i=1}^N$. We denote \mathbb{N}_+ to be the set of positive natural numbers. The concept of scheme for estimation we introduce below can be thought of as a certain general method for obtaining unbiased estimators.

Definition 9. A scheme (of order N) for estimation of generalized estimand G of order N is a pair (t, A) , for a finite set $A \subset \mathbb{N}_+^N$ and a function

$$t : \mathbb{R}^{|A|} \mapsto \mathbb{R}, \quad (4.35)$$

such that

$$\phi(t, A) = t(g_A) \quad (4.36)$$

is generalized unbiased estimator of G with dimensions of arguments n_A .

Estimator $\phi(t, A)$ defined by (4.36) is called estimator corresponding to, or given by scheme (t, A) . For example for generalized estimand V_1^{tot} we introduced earlier in this Section, the scheme (t, A) is defined as follows. We take $A = \{(1, 1), (2, 1)\}$ and

$$t(x_{(1,1)}, x_{(2,1)}) = x_{(1,1)}^2 - x_{(1,1)}x_{(2,1)}. \quad (4.37)$$

Introducing C language-like notation $g_j = g[j_1 - 1] \dots [j_N - 1]$, estimator corresponding to (t, A) can be written as

$$\widehat{V}_{1,a3}^{tot} = g[0][0](g[0][0] - g[1][0]). \quad (4.38)$$

The fact that this is scheme for estimation of V_1^{tot} is a consequence of Theorem 6 and the fact that observable of this estimator corresponding to function f and observable $\tilde{X} = (\tilde{X}_1[j]_{j=0}^1, \tilde{X}_2[0]) \sim \mu^{n_A}$ is

$$f(\tilde{X}_1[0], \tilde{X}_2[0])(f(\tilde{X}_1[0], \tilde{X}_2[0]) - f(\tilde{X}_1[1], \tilde{X}_2[0])). \quad (4.39)$$

We use formulas defining estimators of form like (4.38) to concisely define schemes for estimation. Scheme given by formula like (4.38) is a pair (t, A) , with set A of indices j corresponding to different g_j appearing on the rhs of this formula and t acting on its arguments $(x_j)_{j \in A}$ the same way as function of $(g_j)_{j \in A}$ given by the rhs of formula like (4.38) acts on its arguments.

Note that any estimation scheme (t, A) for estimation of some estimand can be used to generate estimates of its values corresponding to some (f, μ) as follows. One first generates the required values \tilde{X}_j for $j \in A$ and $\tilde{X} \sim \mu^{n_A}$, then computes values of $g_j(f)(\tilde{X}) = f(\tilde{X}_j)$

and finally uses them to compute the value of t on $g_A(f(\tilde{X}))$. We thus call $|A|$ the number of function evaluations used by scheme (t, A) . Such computed values can be used as single-step Monte Carlo estimates. For instance scheme analogous to (4.38) can be used in Monte Carlo procedure estimating V_R^{tot} for some observable $f(P, R)$ of process of DM corresponding to one of its constructions. In our numerical experiments using different schemes, functions f corresponding to different constructions of DM and distributions μ the duration τ_s of a single MC step for the same f and μ and using the same implementation of process simulation algorithm on the same computer is with a good approximation proportional to the number of function evaluations used by different schemes. Let this proportionality constant for given f , μ , implementation and computer be τ_k . The inefficiency constant of a single MC step using scheme (t, A) can be written as

$$c = \text{Var}_{f,\mu}(\phi(t, A))|A|\tau_k. \quad (4.40)$$

Note that if we are interested in estimating variance-based sensitivity index of an observable of DM, whose value does not depend on its construction (see discussion in Section 3.3), then we can use given scheme for different functions f appearing in observables $f(P, R)$ corresponding to different constructions of DM and with $\mu = \mu_P \times \mu_R$ for μ_R corresponding to distributions of noise variables used in these constructions. This may influence the value of $\text{Var}_{f,\mu}(\phi)$. Numerical results and some intuitions concerning these differences of variances for estimators using GD and RTC constructions for different schemes are discussed in Section 4.6. The time τ_k depends not only on the construction of DM used, but also on its computer implementation and even computer architecture, which is discussed in more detail in Section 4.7. For single steps of MC procedures, whose inefficiency constants are approximately of form (4.40), and which use the same functions f with the same distribution μ and the same implementation on the same computer, the ratio of their inefficiency constants is the same as of implementation-independent inefficiency constants defined as

$$d_{t,A}(f, \mu) = \text{Var}_{f,\mu}(\phi(t, A))|A|. \quad (4.41)$$

We call (4.41) inefficiency constant of scheme (t, A) corresponding to f and μ . Similarly as in (4.21) one shows that the ratio of inefficiency constants (4.41) of two different schemes for given μ and f is equal to the ratio of variances of final MC estimators using these schemes for the same number of function evaluations made in both MC procedures.

4.4. Symmetrization of schemes

Let Π_a be the group of bijections, which we also call permutations of set \mathbb{N}_+^N . Subgroup of Π_a consisting of permutations of the i -th coordinate is defined as

$$\Pi_{a,i} := \{\pi \in \Pi_a : \forall j \in \mathbb{N}_+^N \quad (\pi(j))_k = j_k \text{ for } k \neq i\}. \quad (4.42)$$

For two subgroups Π_{s_1}, Π_{s_2} of Π_a we denote $\Pi_{s_1} \cdot \Pi_{s_2}$ to be its subgroup generated by elements $\pi_1\pi_2$, such that $\pi_i \in \Pi_{s_i}$ for $i \in I_2$. Let us consider subgroup Π_b of Π_a defined as $\Pi_b = \Pi_{a,1} \cdot \dots \cdot \Pi_{a,N}$. Let us consider some finite subgroup Π_s of Π_b . For finite set $A \subset \mathbb{N}_+^N$ we define its symmetrization with respect to Π_s as

$$\Pi_s(A) = \{\pi(j) : j \in A, \pi \in \Pi_s\}. \quad (4.43)$$

For function $t : \mathbb{R}^{|A|} \mapsto \mathbb{R}$ we define symmetrization of t with respect to Π_s and A , denoted as $S_{\Pi_s, A}(t)$ to be a function from $\mathbb{R}^{|\Pi_s(A)|}$ to \mathbb{R} , such that

$$S_{\Pi_s, A}(t)((y_j)_{j \in \Pi_s(A)}) = \frac{1}{|\Pi_s|} \sum_{\pi \in \Pi_s} t((y_{\pi(j)})_{j \in A}). \quad (4.44)$$

Symmetrization of scheme (t, A) for estimation of G with respect to Π_s is defined as scheme $(S_{\Pi_s, A}(t), \Pi_s(A))$. The estimator given by $(S_{\Pi_s, A}(t), \Pi_s(A))$ is

$$S_{\Pi_s, A}(t)(g_{\Pi_s(A)}) = \frac{1}{|\Pi_s|} \sum_{\pi \in \Pi_s} t((g_{\pi(j)})_{j \in A}). \quad (4.45)$$

Note that an observable of estimator of symmetrized scheme, corresponding to some f and $\tilde{X} \sim \mu^{n_{\Pi_s(A)}}$, which can be written as

$$\frac{1}{|\Pi_s|} \sum_{\pi \in \Pi_s} t((f(\tilde{X}_{\pi(j)}))_{j \in A}), \quad (4.46)$$

is a sum of random variables with the same distribution. Thus symmetrized scheme is also scheme for estimation of G . We define subgroup of $\Pi_{a,i}$ (4.42) consisting of permutations of first k indices in the i -th coordinate as

$$\Pi_{i,k} = \{\pi \in \Pi_i : \forall j \in \mathbb{N}_+^N \quad (\pi(j))_i = j_i \text{ for } j_i \notin I_k\}. \quad (4.47)$$

Symmetrization of a scheme (t, A) with respect to $\Pi_{i,k}$ for $k \geq n_{A,i}$ is called symmetrization in the i -th argument from $n_{A,i}$ to k dimensions, or if $k = n_{A,i}$ simply symmetrization in the i -th argument. Symmetrization with respect to $\Pi_A = \Pi_{1,n_{A,1}} \times \dots \times \Pi_{N,n_{A,N}}$ is called symmetrization of the scheme in all arguments.

We further need the following well-known Theorem we leave without proof.

Theorem 10. *For $X, Y \in L^2(\mathbb{P})$ and $X \sim Y$ we have that*

$$\text{Cov}(X, Y) \leq \text{Var}(X). \quad (4.48)$$

Equality in (4.48) holds if and only if (iff) $X = Y$.

From theorem below it follows that estimator corresponding to symmetrized scheme has not higher variance than the one given by the original scheme.

Theorem 11. *If random variables $(A_i)_{i=1}^n$ from $L^2(\mathbb{P})$ have the same distribution, then*

$$\text{Var}\left(\frac{1}{n} \sum_{i=1}^n A_i\right) \leq \text{Var}(A_1) \quad (4.49)$$

and equality in (4.49) holds iff $A_i = A_j$ for all $i, j \in I_n$.

Proof. We have

$$\begin{aligned} \text{Var}\left(\frac{1}{n} \sum_{i=1}^n A_i\right) &= \frac{1}{n^2} \sum_{i,j \in I_n} \text{Cov}(A_i, A_j) \\ &\leq \frac{1}{n^2} \sum_{i,j \in I_n} \text{Var}(A_1) = \text{Var}(A_1). \end{aligned} \quad (4.50)$$

Equality in (4.50) holds only if for all $i, j \in I_n$ $\text{Cov}(A_i, A_j)$ is equal to $\text{Var}(A_1)$, which from Theorem 10 occurs iff $A_i = A_j$. \square

The above Theorem could also be proved using Schwarz inequality similarly as in Theorem 5 in [24].

After symmetrization of scheme given by (4.38) in the first argument we receive scheme given by

$$\hat{V}_{1,s2}^{tot} := \frac{1}{2}(g[0][0] - g[1][0])^2. \quad (4.51)$$

It uses the same number of function evaluations, so it has not higher inefficiency constant. Analogously to what we did for total sensitivity index in the last section we can define generalized estimand corresponding to main sensitivity index of a function with some product distribution of arguments with respect to a given argument and specify its domain. Since definitions of such generalized estimands are obvious, we omit them. Using Theorem 6 one can receive the following well-known estimator for main sensitivity index with respect to the first argument

$$\widehat{V}_{1,a3} := g[0][0](g[0][1] - g[1][1]). \quad (4.52)$$

After symmetrization of its scheme in all coordinates we receive scheme given by

$$\widehat{V}_{1,s4} := \frac{1}{2}(g[0][0] - g[1][0])(g[0][1] - g[1][1]). \quad (4.53)$$

Its estimator has not higher variance, but uses 4 rather than 3 function evaluations, so that their respective inefficiency constants fulfill

$$d_{V_{1,s4}} \leq \frac{4}{3}d_{V_{1,a3}}, \quad (4.54)$$

which should be understood as relation valid for all appropriate (f, μ) . For $f(X_1, X_2) = X_1$ and $P(X_1 = 1) = P(X_1 = -1) = 1/2$ the variance of both estimators is equal to 1, so for inefficiency constant corresponding to such specified f and any $\mu \sim (X_1, X_2)$ we have equality in (4.54).

One can get estimator for total sensitivity index using the same function evaluations as (4.53)

$$\widehat{V}_{1,s4}^{tot} := \frac{1}{4} \sum_{i=0}^1 (g[0][i] - g[1][i])^2 \quad (4.55)$$

and also an estimator for variance of f

$$\widehat{D}_{s4} := \frac{1}{4} \sum_{i=0}^1 (g[0][i] - g[1][1-i])^2. \quad (4.56)$$

One may wonder what is the relation between inefficiency constants of schemes for estimation of total sensitivity index given by (4.51) and (4.55). We receive it from the following Theorem.

Theorem 12. *Let us consider scheme (t_2, A_2) of some order N created from (t_1, A_1) by its symmetrization in the i -th argument from 1 to 2 dimensions. Then their inefficiency constants fulfill*

$$d_{t_1, A_1} \leq d_{t_2, A_2} \leq 2d_{t_1, A_1}. \quad (4.57)$$

Proof. Let ϕ_i for $i \in I_2$ be estimators given by corresponding schemes. We have $(A_1)_i = \{1\}$ and $(A_2)_i = \{1, 2\}$. For some observable $\tilde{X} \sim \mu^{n_{A_2}}$ we denote $\tilde{V} := \tilde{X}_i$ as in (4.30), and $\tilde{U} := (\tilde{X}_j)_{j \in I_N, j \neq i}$. We have

$$\phi_2(f)(\tilde{X}) = \frac{1}{2}(\phi_1(f)(\tilde{U}, \tilde{V}_1) + \phi_1(f)(\tilde{U}, \tilde{V}_2)). \quad (4.58)$$

Taking variance of the rhs of (4.58) we get

$$\frac{1}{2}(\text{Var}_{f,\mu}(\phi_1) + \text{Cov}(\phi_1(f)(\tilde{U}, \tilde{V}_1), \phi_1(f)(\tilde{U}, \tilde{V}_2))). \quad (4.59)$$

From Theorem 6 it follows that the last covariance is equal to $\text{Var}(\mathbb{E}(\phi_1(f)(\tilde{U}, \tilde{V}_1)|\tilde{U}))$. Thus from the fact that

$$0 \leq \text{Var}(\mathbb{E}(\phi_1(f)(\tilde{U}, \tilde{V}_1)|\tilde{U})) \leq \text{Var}_{f,\mu}(\phi_1) \quad (4.60)$$

variances of these estimators fulfill

$$\frac{1}{2} \text{Var}_{f,\mu}(\phi_1) \leq \text{Var}_{f,\mu}(\phi_2) \leq \text{Var}_{f,\mu}(\phi_1). \quad (4.61)$$

Since $|A_2| = 2|A_1|$ from (4.41) we receive (4.57). \square

Scheme (4.55) is received from (4.51) by symmetrization in the 2-nd argument from 1 to 2 dimensions, thus from the above Theorem we receive

$$d_{V_1^{tot},s2} \leq d_{V_1^{tot},s4} \leq 2d_{V_1^{tot},s2}. \quad (4.62)$$

4.5. Schemes for estimation of sensitivity indices with respect to many arguments

We can be interested in estimating values of many estimands simultaneously, e. g. main variance-based sensitivity indices of output of a model with respect to all its parameters in order to decide which of them to measure experimentally, as discussed in Section 3.5. Let us consider MC procedure, in which N different schemes equal to coordinates of $S = ((A_i, t_i))_{i=1}^N$ are used in a single MC step for estimation of $\lambda_1, \dots, \lambda_N$. We call S scheme for estimation of $\lambda_1, \dots, \lambda_N$. (A_i, t_i) is called the sub scheme of S for estimating λ_i . We define inefficiency constant of S in estimating λ_i for $i \in I_N$, as

$$d_{\lambda_i, S}(f, \mu) = \left| \bigcup_{i=1}^N A_i \right| \text{Var}_{f,\mu}(\phi(A_i, t_i)), \quad (4.63)$$

where $\phi(A_i, t_i)$ is estimator corresponding to (A_i, t_i) . $\left| \bigcup_{i=1}^N A_i \right|$ is equal to the number of function evaluations required for computing estimates of all estimands, using this scheme. Constant (4.63) has similar interpretations as inefficiency constants of schemes for estimation of single estimands, as discussed in the previous Section. One could also use some measures of inefficiency of the scheme in estimating all estimands, e. g. certain weighted sum of the above defined inefficiency constants, but we further focus only on constants (4.63). Relations we derive here for (4.63) for different schemes can be used to derive similar relations for weighted sums.

We now describe a scheme for estimation of all main and total sensitivity indices of functions $f(P)$ of some vector $P = (P_i)_{i=1}^{N_P} \sim \mu$ with independent coordinates (assuming $f(P) \in L^2(\mathbb{P})$), where the sensitivities are computed with respect to individual coordinates. This scheme was used in [64] for sensitivity analysis of a deterministic chemical kinetic model. Let $\tilde{P} = (\tilde{P}[i])_{i=0}^1$, where $\tilde{P}[i] = (\tilde{P}_j[i])_{j=1}^{N_P}$ for $i \in \{0, 1\}$ are independent copies of P . Let further $\tilde{P}_k = (\tilde{P}_k[i])_{k=0}^1$ and $\tilde{P}_{(k)}[i]$ be equal to vector $\tilde{P}[i]$ with k -th coordinate replaced by $\tilde{P}_k[1-i]$. For $i \in \{0, 1\}$ we introduce helper functions

$$s[i](f)(\tilde{P}) = f(\tilde{P}[i]), \quad (4.64)$$

$$s_k[i](f)(\tilde{P}) = f(\tilde{P}_{(k)}[i]), \quad (4.65)$$

which are just convenient notation for certain functions g_j defined by (4.31). The scheme for estimation of main sensitivity index with respect to k -th argument in O is given by

$$\hat{V}_{k,O} = \frac{1}{2} (s[0] - s_k[0])(s_k[1] - s[1]), \quad (4.66)$$

while for the total sensitivity index by

$$\hat{V}_{k,O}^{tot} = \frac{1}{4} \sum_{i=0}^1 (s[i] - s_k[i])^2. \quad (4.67)$$

One can also estimate a number of further indices using the same function evaluations, see [64] for schemes for estimation of sensitivity indices with respect to pairs of parameters and for variance of $f(P)$. For $N_P > 2$ this scheme requires $2(N_P + 1)$ function evaluations, while for $N_P = 2$ only $2N_P$, since we have $s_1[i] = s_2[1 - i]$. For $N_P = 3$ one can find schemes with lower inefficiency constants in estimating all of these indices, given that the original constants were nonzero. We discuss it in Appendix C. For estimation of only total sensitivity indices one receives not higher inefficiency constant when using following estimator for each k -th parameter

$$\widehat{V}_{k,OT}^{tot} = \frac{1}{2}(s[0] - s_k[0])^2. \quad (4.68)$$

The relation between efficiency constants of schemes given by (4.67) and (4.68) is, for all $k \in I_{N_P}$

$$d_{V_k^{tot},OT} \leq d_{V_k^{tot},O} \leq 2d_{V_k^{tot},OT}, \quad (4.69)$$

since for fixed k (4.67) is received from (4.68) by symmetrization from 1 to 2 dimensions in the second argument if f is treated as function of two arguments corresponding to values of random variables P_k and $P_{\sim k}$.

Let us now focus on functions of form $f(P, R)$, for P as before and random variable R independent of P . $f(P, R)$ can be for instance observable of DM, corresponding to its certain construction and noise term R . Let us take \tilde{P} as before and $\tilde{R} = (\tilde{R}[i])_{i=0}^1$, where $\tilde{R}[i]$ are independent copies of R , independent of \tilde{P} . We now present different new schemes for estimation of both main and total sensitivity indices of conditional expectation of $\mathbb{E}(f(P, R)|P)$ with respect to individual parameters, pairs (P_i, P_j) and a number of other indices. We define

$$s[i][j](f)(\tilde{P}, \tilde{R}) = f(\tilde{P}[i], \tilde{R}[j]) \quad (4.70)$$

and

$$s_k[i][j](f)(\tilde{P}, \tilde{R}) = f(\tilde{P}_{(k)}[i], \tilde{R}[j]). \quad (4.71)$$

We use notation

$$\tilde{s}[i][j] := s[i][j](f)(\tilde{P}, \tilde{R}) \quad (4.72)$$

to denote the observable of this estimator corresponding to f and variables \tilde{P} \tilde{R} and analogically for $\tilde{s}_k[i][j]$. We also denote observable of a generalized estimator of λ_i from scheme $S \lambda_{i,S}(f)(\tilde{P}, \tilde{R})$ simply as $\lambda_{i,S}$. For $f(P, R)$ we define indices like V_{P_k} , $\tilde{V}_{P_k}^{tot}$, D and V_P in the same way as in Section 3.3 for observables of DM. The fact that schemes for estimation of individual indices given by formulas below are unbiased is an easy consequence of Theorem 6 and expressions for respective sensitivity indices derived in Section 3.3. We first define a C language-like notation

$$(a == b)?c : d = \begin{cases} c & \text{if } a = b, \\ d & \text{otherwise,} \end{cases} \quad (4.73)$$

and helper functions

$$A_M(s, l, r) = \frac{1}{4} \sum_{i=0}^1 \sum_{j=0}^1 s[i][j] s[(l == 1)?i : (1 - i)][(r == 1)?j : (1 - j)], \quad (4.74)$$

$$B_M(s, s_k, l, r) = \frac{1}{4} \sum_{i=0}^1 \sum_{j=0}^1 s[i][j] s_k[(l == 1)?i : (1 - i)][(r == 1)?j : (1 - j)]. \quad (4.75)$$

For $k \in I_{N_P}$ we define

$$\begin{aligned} \widehat{V}_{k,E} &:= B_M(s, s_k, 0, 0) - \frac{A_M(s, 0, 0) + A_M(s_k, 0, 0)}{2} \\ &= \frac{1}{4} \sum_{i=0}^1 (s[i][0] - s_k[i][0])(s_k[1 - i][1] - s[1 - i][1]), \end{aligned} \quad (4.76)$$

$$\begin{aligned}\widehat{\tilde{V}}_{k,E}^{tot} &:= \frac{A_M(s, 1, 0) + A_M(s_k, 1, 0)}{2} - B_M(s, s_k, 1, 0) \\ &= \frac{1}{4} \sum_{i=0}^1 (s[i][0] - s_k[i][0])(s[i][1] - s_k[i][1]).\end{aligned}\tag{4.77}$$

$$\widehat{D}_E := \frac{1}{(N_P + 1)} (A_M(s, 1, 1) - A_M(s, 0, 0) + \sum_{k=1}^{N_P} A_M(s_k, 1, 1) - A_M(s_k, 0, 0)), \tag{4.78}$$

$$\widehat{V}_{P,E} := \frac{1}{(N_P + 1)} (A_M(s, 1, 0) - A_M(s, 0, 0) + \sum_{k=1}^{N_P} A_M(s_k, 1, 0) - A_M(s_k, 0, 0)), \tag{4.79}$$

$$\widehat{V}_{R,E}^{tot} := \widehat{D}_E - \widehat{V}_{P,E}. \tag{4.80}$$

Using the same function evaluations we can also construct schemes for estimation of many further indices, among others for $V_{(P_i, P_j)}$ and $\widetilde{V}_{(P_i, P_j)}^{tot}$, which we describe in Appendix B. The scheme for estimation of sensitivity indices of conditional expectation consisting of individual schemes given by formulas above is called scheme E. It uses $4(N_P + 1)$ function evaluations for $N_P > 2$ and $4N_P$ for $N_P = 2$, since in the last case we have

$$s_2[j][i] = s_1[1 - j][i]. \tag{4.81}$$

For $N_P = 3$ there exists more efficient scheme as discussed in Appendix C.

Scheme EM, which can have lower inefficiency constants in estimating main sensitivity indices of conditional expectations consists of sub schemes given by, for $k \in I_{N_P}$

$$\widehat{V}_{k,EM} = \frac{1}{2} (s[0][0] - s_k[0][0])(s_k[1][1] - s[1][1]). \tag{4.82}$$

Scheme EM uses two times fewer function evaluations than E, for $N_P > 2$. In Appendix B we prove the following Theorem.

Theorem 13. *Inefficiency constants of scheme EM and E for estimation of V_i fulfill, for $N_P > 2$*

$$d_{V_i,EM} \leq d_{V_i,E} \leq 2d_{V_i,EM}. \tag{4.83}$$

Due to proportionality of number of function evaluations used by schemes for all indices and schemes for individual indices, the same inequalities hold also for the latter. We can extend this scheme to scheme EMe which uses additional functions in $(s[i][1 - i])_{i=0}^1$ in sub schemes for total sensitivity indices of the mean, for $k \in I_{N_P}$

$$\widehat{\tilde{V}}_{k,EMe}^{tot} := \frac{1}{2} \sum_{i=0}^1 (s[i][i]s[i][1 - i] - s_k[i][i]s[i][1 - i]). \tag{4.84}$$

Scheme ET, which can be potentially more efficient for estimation of total sensitivity indices, contains schemes

$$\widehat{\tilde{V}}_{k,ET}^{tot} := \frac{1}{2} (s[0][0] - s_k[0][0])(s[0][1] - s_k[0][1]), \tag{4.85}$$

for $k \in I_{N_P}$, which use together two times fewer function evaluations than scheme E, for $N_P > 2$. We have the following relations

$$d_{\tilde{V}_i^{tot},ET} \leq d_{\tilde{V}_i^{tot},E} \leq 2d_{\tilde{V}_i^{tot},ET} \tag{4.86}$$

and analogically for inefficiency constants of their sub schemes for estimating these indices. This is a consequence of the fact that if arguments of f corresponding to coordinates of $\tilde{P}_{\sim k}[0]$ are treated as a single argument, then scheme defining $\tilde{V}_{i,E}^{tot}$ is symmetrization of scheme defining $\tilde{V}_{i,ETe}^{tot}$ from 1 to 2 dimensions in this argument. We can extend scheme ET to ETe by adding to it sub schemes for estimation of main sensitivity index of conditional mean, given by formula

$$\hat{\tilde{V}}_{k,ETe} := \frac{1}{2} \sum_{i=0}^1 (s_k[0][i]s[1][1-i]) - A_M(s, 0, 0), \quad (4.87)$$

which additionally needs functions $(s[i][i])_{i=0}^1$. The number of function evaluations used by schemes EMe and ETe is $\frac{N_P+2}{N_P+1}$ times this number for schemes EM and ET. Since scheme defining $\hat{\tilde{V}}_{k,E}$ is symmetrization of $\hat{\tilde{V}}_{k,ETe}$ in the argument corresponding to P_k in $f(P, R)$, we receive the following relationship for $N_P > 2$

$$2 \frac{N_P + 1}{N_P + 2} d_{V_k,ETe} \geq d_{V_k,E} \quad (4.88)$$

and analogically for schemes defining $\hat{\tilde{V}}_{k,E}$ which is symmetrization of scheme defining $\hat{\tilde{V}}_{k,EMe}^{tot}$ with respect to the same group. In numerical examples we will see that $d_{V_k,ETe}$ can be much higher than $d_{V_k,E}$ and analogously for $d_{\tilde{V}_k^{tot},EM}$ and $d_{\tilde{V}_k^{tot},E}$. Let us also notice, that for functions of additive form

$$f(P, R) = f_1(P) + f_2(R) \quad (4.89)$$

observables of estimators (4.76) and (4.82) corresponding to the same \tilde{P} are equal for every $k \in I_{N_P}$. In particular they have the same variances and we have equality in the right inequality of relation (4.83). If further for $f_1(P)$ from (4.89) it holds

$$f_1(P) = \sum_{i=1}^{N_P} f_{1,i}(P_i) \quad (4.90)$$

then also appropriate observables of estimators (4.77) and (4.85) are identical and we have equality in the right inequality of relation (4.86).

All the schemes for estimation of sensitivity indices of conditional expectations introduced in this Section can be also used for conditional histograms, except that instead of using real-valued observables one should use their vector-valued single-sample histograms and instead of function multiplication use scalar product of vectors. This is a consequence expression (3.41) after the proof of Theorem 6.

4.6. Variances of estimators for different constructions of DM

If two estimators are unbiased the relation between their variances is the same as between the expectations of their squares. Let $h(p, R)$ be certain construction of DMCP (1.15) and $f(p, R) = g(h(p, R))$ its observable. In each step of MC simulations performed in [49] the values of independent copies of an observable $f(p, R)$, representing the number of particles of certain species at a given moment of time, were generated for the nominal parameter value p and the values of copies of observable $f(p + he_i, R)$ for some small perturbation h of the i -th coordinate of p , for the purpose of estimating finite differences of means

$$\frac{1}{|h|} \mathbb{E}(f(p + he_i, R) - f(p, R)). \quad (4.91)$$

The computed estimates of the following expectation

$$\text{err}(p, p + e_i h) = \mathbb{E}((f(p, R) - f(p + e_i h, R))^2), \quad (4.92)$$

which influences the variance of estimators they used, were much lower when performing simulations with RTC construction, rather than GD construction. We call this effect tighter coupling between the value of the considered observable to the noise term for the nominal and perturbed values of parameters for RTC than for GD algorithm. Reader is referred to the original work [49] for a number of intuitions supporting this effect. Chemical reaction networks for which this effect was observed contained reactions influencing the investigated particle numbers in different ways, for instance in some reactions the number of particles increased, while in others it decreased. Let us assume that for such reaction networks, for all p_1 and p_2 in the image of P , $\text{err}(p_1, p_2)$ is greater for the same observables constructed using GD than RTC method. Since for an observable of estimator (4.82) we have, using notations from previous Section

$$\begin{aligned} 4\mathbb{E}((V_{k,EM})^2) &= \mathbb{E}((\tilde{s}_k[0][0] - \tilde{s}[0][0])^2(\tilde{s}[1][1] - \tilde{s}_k[1][1])^2) \\ &= \mathbb{E}((\mathbb{E}^2(f(p_{k,0}, \tilde{R}[0]) - f(p_0, \tilde{R}[0])) \\ &\quad \cdot \mathbb{E}^2(f(p_1, \tilde{R}[1]) - f(p_{k,1}, \tilde{R}[1])))_{p_j=\tilde{P}[j], p_{k,j}=\tilde{P}_{(k)}[j], j \in \{0,1\}}) \\ &= \mathbb{E}(\text{err}(\tilde{P}_{(k)}[0], \tilde{P}[0]) \text{err}(\tilde{P}[1], \tilde{P}_{(k)}[1])), \end{aligned} \quad (4.93)$$

so with the assumption made this should be greater for GD than RTC construction. Although we could not confirm whether this assumption is true, the decrease of estimated variance of estimator (4.82) was indeed confirmed in all our numerical experiments involving chemical reaction networks containing reactions influencing particle numbers in different ways. Denoting $A[i] = \frac{1}{4}(\tilde{s}[i][0] - \tilde{s}_k[i][0])(\tilde{s}_k[1-i][1] - \tilde{s}[1-i][1])$ we have that an observable of estimator (4.76) fulfills

$$\mathbb{E}((V_{k,E})^2) = \mathbb{E}\left(\left(\sum_{i=0}^1 A[i]\right)^2\right) = 2(E((V_{k,EM})^2) + \text{Cov}(A[0], A[1])). \quad (4.94)$$

The estimates of $\text{Cov}(A[0], A[1])$ from our numerical experiments sometimes decreased and sometimes increased when going from GD to RTC construction, but we nevertheless always observed the decrease of the estimated value of $\mathbb{E}((V_{k,E})^2)$. Note that observable of estimator (4.85) fulfills

$$4\mathbb{E}((\tilde{V}_{k,ET}^{tot})^2) = \mathbb{E}(\text{err}(\tilde{P}_{(k)}[0], \tilde{P}[0])^2), \quad (4.95)$$

so we could suspect it should also have lower variance for RTC than GD method and this was indeed confirmed in our numerical experiments. Intuitions and numerical results for the estimator of total sensitivity index of mean from scheme E (4.77) were analogical as in case of the main index.

Note that although change of order of the indices of reactions in a chemical reaction network does not influence the variance of the estimators using RTC construction, as only reorders the Poisson processes in the construction, it might have impact on the variance of estimators when using GD algorithm. We had an intuition that grouping reactions having similar influence on the output together in the sequence of reactions used by GD construction should lead to tighter coupling between the observables and the noise term for different values of parameters, and thus to lower variances of estimators we discussed in this Section, than when reactions with opposing effects appear in the sequence one after another. This is because we suspected that reactions lying close to one another in the sequence may often be fired in the same step of constructions using two different values of parameters and the same noise term. We will see this effect confirmed in Section 5.3, in a numerical experiment specially designed for testing it.

4.7. Implementation

All our numerical experiments were performed using a program written in C++ language, run on a personal computer with 1GB RAM, 2-core 2.10 Hz processor and with Linux operating system. For random number generation we used Gnu Scientific Library (GSL) [20] implementation of Mersenne twister random number generator (RNG) [36]. Using notations from Section 4.5, at the beginning of each Monte Carlo step we generated value of an independent copy of a variable P . Observables of functions needed by a given scheme were generated by running given simulation algorithm starting with appropriate parameters and reusing the same generated values of artificial noise variable $\tilde{R}[j]$ to compute values of observables $\tilde{s}[i][j]$ and $\tilde{s}_{(k)}[i][j]$ for the same $j \in \{0, 1\}$. We describe different strategies for reusing values of these variables later on in this Section.

We used simple implementations of GD method and RTC algorithm, that is we used arrays to store reaction states and propensities as well as linear search for minimum to obtain S_{i+1} in RTC construction, or reaction to fire in GD method. Often simplest implementations turn out to be the fastest when simulating small reaction networks, whereas smaller computation time can be achieved for more complex networks when using improvements like dependency graphs, sparse arrays, priority queues or dynamical reordering of reactions in GD method [39]. See [37] for a recent review and comparison of computation times of simulations using a variety of different data structures. Most of these enhancements can be incorporated into our algorithms without changing the variance of resulting estimators, but some, like dynamically changing the order of reactions in GD algorithm may have impact on the variance.

We numerically investigated two different approaches to reusing values of each independent copy of the noise variable needed in a single Monte Carlo step. Similar methods were suggested in [49] for performing local sensitivity analysis, where, however, only the first method was tested numerically. In the first method, in addition to the main RNG used for generating parameters, one uses separate RNGs for simulating the noise variables, one RNG in the GD method and one RNG for every independent Poisson process in the RTC method. In order to retrieve the same values of artificial noise variable $\tilde{R}[j]$ one reuses the same initial seeds of RNGs for noise variables, which are chosen randomly at the beginning of the Monte Carlo step from the possible RNG seed range, using the main RNG. The drawback of this method is that one needs to generate the same random numbers and to reinitialize RNGs for noise variables several times in each Monte Carlo step. In the second approach one stores the values of the same independent noise term in a separate set of lists. In GD method one uses single list for every noise variable, while in RTC method different one for every Poisson process. New values are added to the lists when needed and new memory is allocated to make the list longer only when more random numbers are produced for a given list than in previous Monte Carlo steps. The disadvantage of this method is that one needs additional memory for the lists and uses up time for reading from and writing onto them. Fortunately, we did not experience any memory exhaustion problem in our numerical experiments.

We compared the average execution time of MC procedures using scheme E from Section 4.5 on three chemical reaction networks, which we define in Chapter 5 and for the two mentioned approaches to reusing the values of noise variables. The results are presented in Table 4.1. We can see that the first approach was from 5% to 89% slower. When the reinitialization of RNG was commented out we observed that the first approach was on average only from 4% to 7% slower in all examples (data not shown), thus high relative increase of cost for instance in the MBMD model can be explained by the significant contribution of the RNG reinitialization to the overall cost of a single simulation due to the single simulation being rather short. The data presented in the further Sections was produced using only the second approach.

From Table 4.1 we can also see that the execution times of simulations using GD and

DM	RTC_l	RTC_{nl}	% inc.	GD_l	GD_{nl}	% inc.
SB	97.13 ± 0.49	111.8 ± 1.7	15%	103.65 ± 0.60	122.07 ± 0.71	18%
GTS	130.73 ± 0.48	137.17 ± 0.26	4.9%	132.07 ± 0.10	138.94 ± 0.22	5.2%
MBMD	110.32 ± 0.04	208.02 ± 0.86	89%	107.60 ± 0.09	129.66 ± 0.56	21%

Table 4.1: The Table presents mean execution times in seconds of MC procedures using scheme E for observables of simple birth (SB), genetic toggle-switch (GTS) and many births - many deaths (MBMD) models defined in Chapter 5. RTC and GD algorithms were used both with and without lists for reusing artificial noise variables (denoted by subscripts l and nl respectively). 50000 steps were performed for SB and MBMD models and 5000 for GTS. The means were computed from 3 runs with random initial seeds and are given with estimates of standard errors. The “% inc.” column contains the relative increases of estimated mean duration times of MC procedure without lists over the one with lists.

RTC methods and the approach with lists were approximately the same for all models.

4.8. Quasi-Monte Carlo and variance reduction methods

One can often speed up the computation of integrals by using quasi-Monte Carlo (QMC) or different variance-reduction techniques rather than ordinary MC method. In QMC method one generates vectors from n -dimensional cube $[0, 1]^n$ for some fixed n in each step of the method using a quasi-random number generator (QRNG) and uses them in the same way as values of observables in form of random vectors $U = (U_i)_{i=1}^{N_P}$ with independent coordinates with distribution $U(0, 1)$ in ordinary MC. For DM with independent parameters $P \sim \mu_1 \times \dots \times \mu_{N_P}$ one can often find functions g_i for $i \in I_{N_P}$, such that $(g_i(U_i))_{i=1}^{N_P} \sim P$. For instance for the case of $P_i \sim U(a_i, b_i)$ one can use

$$g_i(x) = x(b_i - a_i) + a_i, \quad (4.96)$$

while for $P_i \sim U_d(a_i, b_i)$

$$g_i(x) = \lfloor x(b_i - a_i + 1) \rfloor + a_i, \quad (4.97)$$

where for $x \in \mathbb{R}$ its floor $\lfloor x \rfloor$ denotes the biggest integer smaller than or equal to x . We use the QMC for the parameters and MC for the noise variable approach, which relies on using vectors generated with the help of QRNG and above functions to sample parameters and ordinary RNG to sample the artificial noise variable. We call it hybrid QMC-MC approach. One could use QRNG to sample certain number of components of the artificial noise variable as well, but not this whole variable, as we do not know in advance how many of its components are needed in a simulation. A problem with using QMC is that although it usually leads to smaller error than MC there are currently no well-established methods for obtaining error estimates of the result from simulation data [44]. Such error estimates can be obtained by variance-reduction techniques like randomized-quasi Monte Carlo [44], which we however do not test in this work.

4.9. The method of Degasper et al.

We now present generalization of method of Degasper et al. [13], which we already mentioned in the Introduction and Section 2.5. Let us assume that DM has N_P independent parameters $P = (P_i)_{i=1}^{N_P}$, which can be mapped from variables with distributions $U(0, 1)$ as discussed in the previous Section. Replacing original parameters with these mapped variables when necessary, we assume that $P_i \sim U(0, 1)$ for $i \in I_{N_P}$. For m natural positive, called grid level, we define discretized parameter vector D , also called parameter grid, as

a function $D = (D_i)_{i=1}^{N_P} : I_m^{N_P} \mapsto \mathbb{R}^{N_P}$, whose coordinates, called discretized parameters, satisfy for any $j = (j_i)_{i=1}^{N_P} \in I_m^{N_P}$

$$D_i[j] = \frac{j_i}{m+1}. \quad (4.98)$$

Let us assume we estimate sensitivity indices associated with conditional expectation $\tilde{f}(P)$ for some observable $f(P, R) \in L^2(\mathbb{P})$. For some N_s natural positive, called number of simulations in each point of the grid, and independent copies of noise variable $R[j][k] \sim R$ for every $j \in I_m^{N_P}$ and $k \in I_{N_s}$ one computes in a simulation the value of $f(D[j], R[j][k])$. Then one computes discretized estimate of $\tilde{f}(P)$ for every $j \in I_m^{N_P}$

$$\tilde{f}(D[j]) = \phi_{ave} \left((f(D[j], R[j][k](\omega))_{k \in I_{N_s}} \right). \quad (4.99)$$

Now one treats D as a random vector on the discrete probability space $I_m^{N_P}$ with equal probabilities of its elements and performs exact variance-based sensitivity analysis on function $\tilde{f}(D)$. Firstly, one computes conditional expectations of $\tilde{f}(D)$ given certain sub vectors of D , for $J \subset I$ and $v_J \in I_m^J$

$$\mathbb{E}(\tilde{f}(D)|D_J)(v_J) = \frac{1}{m^{|J|}} \sum_{j \sim J \in I_m^J} \tilde{f}(D[v_J, j \sim J]). \quad (4.100)$$

Secondly, one computes variances of these conditional expectations needed to calculate the desired variance-based sensitivity indices of $\tilde{f}(D)$ with respect sub vectors of D . They are used to approximate the sensitivity indices of $\tilde{f}(P)$ given the corresponding sub vectors of P . When approximating sensitivity indices associated with conditional histograms, the procedure is the same, except that one should use unbiased estimator or average histogram, like mean of histogram functions instead of ϕ_{ave} in (4.99). Degasperi et. al. used this method for computing variance based-sensitivity indices of conditional histograms using variance defined with Manhattan distance as discussed in Section 2.5. In the next Section we apply this method to conditional expectations with standard variance and call it shortly grid-based method. Unfortunately, the method presented here does not provide error estimates for the computed approximations of sensitivity indices.

Chapter 5

Numerical experiments

5.1. Simple birth model

We first apply presented methods to a simple birth (SB) model, for which analytical expressions for most of the variance-based sensitivity indices can be obtained. This allows for estimation of mean square errors of approximation of variance-based sensitivity indices using grid-based method described in Section 4.9 and hybrid QMC-MC approach discussed in Section 4.8. The reaction network contains one species X and one birth reaction can occur



It is described by a kinetic formula $a_1(K)(x) = K_1 + K_2 + K_3$, where $K = (K_1, K_2, K_3)$ is a random vector with independent coordinates with uniform respective marginal distributions $U(0.3, 0.9)$, $U(0.85, 1.15)$ and $U(0.07, 0.13)$. Variable C describing initial number of particles of species X has uniform discrete distribution $U_d(30, 90)$ and is independent of K . Note that for this reaction network as well as for the ones in further numerical examples assumptions of Theorem 1 are satisfied for every values of parameters when we take m_i equal to 1 for every i -th species. The observable taken for sensitivity analysis is the number of species X at time $t = 100$. In Appendix D we derive analytical expressions for some of the variance-based sensitivity indices of this observable and its conditional expectation given the parameters. The values obtained from analytic expressions are presented in Table 5.1. For a reaction network with one reaction there is no difference in variance of estimators using GD and RTC algorithms and we use only the latter one.

We performed a 50000 step MC procedure using scheme E. The results, presented in Table 5.2 are in good agreement with analytically computed values from Table 5.1. We also performed computations with grid-based method with grid level 10 and 100 simulations in every point of the grid, which also requires one million simulations in total. From the results in table 5.3 we can see, that although the ordering of values of sensitivity indices computed with this method is correct, these values are much farther from exact ones than for MC procedure.

We performed an experiment comparing mean square errors of grid-based method and MC procedure using scheme E as before, hybrid QMC-MC method using scheme E in 50000 steps and MC procedures using schemes EMe and ETe in 100000 steps. For quasi-Monte Carlo sampling in the parameter space in the hybrid QMC-MC approach we show only data obtained using the Niederreiter quasi-random sequences [7], but using Sobol or Helton sequences, all available from GSL [20], lead to approximately the same results. All methods except for MC procedures using schemes EMe and ETe involved 1 million process simulations and had approximately the same duration. MC using shemes EMe and ETe involved 1.2 times more simulations, but when we consider only their sub schemes EM and ET, they used 1 million simulations as well. Thus from discussion in Section 4.3 the ratio of variances of final MC estimators for all sensitivity indices using schemes E and sub schemes

EM and ET are the same as of their respective inefficiency constants (4.41). We run each method a number of times using the same random number generators without reinitializing, but for hybrid method reinitializing each time the QRNG. In every i -th step we computed an estimate err_i of mean square error of a given method. For MC methods the estimate of err_i was estimate of variance of final MC estimator (4.13). For grid-based and hybrid QMC-MC methods, in which the estimate of sensitivity index with analytically computed value λ in the step was D_i , we took

$$\text{err}_i = (D_i - \lambda)^2. \quad (5.2)$$

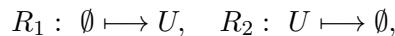
The estimates of mean square error of each method and standard deviation of the result were obtained using mean (4.6) and variance of mean (4.8) estimators applied to sequence of errors from all steps as in MC method. Each method was run 5 times, except for hybrid method, which was run 50 times due to relatively high estimated values of standard deviation of its samples of mean square error. The results are given in Table 5.4. We can see that the estimated mean square error of grid-based method for estimation of sensitivity indices is about three orders of magnitude higher than for pure MC methods using E for all indices, EM for main and ET for total sensitivity indices. The estimate of mean square error of the hybrid method in approximating V_C is even about 50 million times lower than for the grid-based method, but for index V_{K_3} hybrid method does not seem to have any advantage over ordinary MC using scheme E. It can be seen that computed variances of final MC estimators using schemes EMe for total and ETe for main sensitivity indices are much higher than variances for estimators from other schemes and for the same indices, even though the latter used fewer process simulations. Notice also, that estimates of variance of final MC estimators given by scheme EM are approximately two times lower than for scheme E for all main indices and similarly for schemes E and ET for total indices. This coincides with equalities in the right inequalities of relations (4.83) and (4.86). The estimated mean value of the model output and different measures of its dispersion we discussed in Section 3.4 are given in Table 5.5, along with these values for models from the following Sections.

i	\tilde{V}_i	\tilde{V}_i^{tot}	\tilde{S}_i	\tilde{S}_i^{tot}
C	310	310	0, 451	0, 451
K_1	300	300	0, 436	0, 436
K_2	75	75	0, 109	0, 109
K_3	3	3	0, 0044	0, 0044
i	V_i	V_i^{tot}	S_i	S_i^{tot}
P	688		0.80	
R		170		0.20
P, R	858	858	1	0

Table 5.1: Values of sensitivity indices in the SB model obtained from analytic formulas derived in Section D

5.2. Genetic toggle switch model

We now deal with a more biologically interesting model of a genetic toggle switch (GTS). It is a simplified stochastic version of a model of a synthetic genetic toggle switch from [21], which was introduced and used for local sensitivity analysis in [49]. The toggle switch consists of two promoters and their respective repressors U and V . Each promoter is inhibited by a repressor transcribed by the opposing promoter. The following reactions can occur



i	\tilde{V}_i	\tilde{V}_i^{tot}	\tilde{S}_i	\tilde{S}_i^{tot}
C	312.6 ± 1.6	312.6 ± 1.6	0.45	0.45
k_1	301.4 ± 1.6	301.4 ± 1.6	0.44	0.44
k_2	74.04 ± 0.41	74.03 ± 0.41	0.11	0.11
k_3	3.003 ± 0.020	2.992 ± 0.020	0.0043	0.0043
i	V_i	V_i^{tot}	S_i	S_i^{tot}
P	690.4 ± 2.5	701.6 ± 2.5	0.8	0.82
R	159.2 ± 1.0	170.4 ± 1.0	0.18	0.2
P, R	860.8 ± 2.7	860.8 ± 2.7	1	1

Table 5.2: Estimates of sensitivity indices for the SB model computed in a 50000 step MC procedure using RTC algorithm and scheme E.

i	\tilde{V}_i	\tilde{V}_i^{tot}
X	250.8	252.3
K_1	245.9	247.5
K_2	61.29	62.87
K_3	2.393	3.97
P	562.1	562.1

Table 5.3: Estimates of sensitivity indices for SB model computed using grid-based method with 100 simulations in every point of a level 10 grid.

$$R_3 : \emptyset \longmapsto V, \quad R_4 : V \longmapsto \emptyset.$$

Denoting $x = (x_1, x_2)$ the vector of numbers of species U and V respectively, the propensities of the above reactions can be written as

$$a_1(x) = \frac{\alpha_1}{1 + x_2^\beta}, \quad a_2(x) = x_1,$$

$$a_3(x) = \frac{\alpha_2}{1 + x_1^\gamma}, \quad a_4(x) = x_2.$$

The values of rate constants in [49] were $\alpha_1 = 50$, $\alpha_2 = 16$, $\beta = 2.5$ and $\gamma = 1$. We consider each rate constant with above mentioned value v to be a random variable with distribution $U(0.8v, 1.2v)$ and independent of other constants. Similarly as in [49] the initial particle numbers of both species were set to 0 and the observable considered for sensitivity analysis was the number of particles of species U at time $t = 10$. In Table 5.6 we present estimates of sensitivity indices computed from a 50000 step MC procedure using scheme E. From Table 5.6 we can see that the parameter with the greatest values of estimates of both main and total indices for conditional mean is α_1 , while the lowest estimates of indices are these of parameter β . In Table 5.7 we present estimates of variances of final MC estimators of procedures using RTC algorithm and GD method with 2000 steps for scheme E and 4000 for EMe and ETe, so that the variances are computed for the same number of process simulations used by certain schemes, similarly as in the previous Section. The estimates were obtained from 50 independent runs of each of these methods. The estimated variances are lower for RTC than GD method for all main and total indices, in agreement with discussion in Section 4.6. They are even about 4 times lower for the indices associated with parameter β . Notice also that estimates of variances of final MC estimators given by scheme EM are not much lower than for scheme E for all main indices and similarly for schemes E and ET for total indices, which is close to theoretical bounds given by equalities in the left inequalities of relations (4.83) and (4.86).

i	Grid	E	E-QMC	EMe	ETe
	err \tilde{V}_i^{tot}				
C	3464 ± 23	2.6922 ± 0.0061	$7.1 \pm 1.6 \cdot 10^{-5}$	1.3437 ± 0.0019	333.29 ± 0.38
K_1	2986 ± 19	2.696 ± 0.012	0.224 ± 0.046	1.3687 ± 0.0053	327.15 ± 0.18
K_2	184.9 ± 2.1	0.1754 ± 0.0016	0.168 ± 0.029	0.09212 ± 0.00037	83.420 ± 0.065
K_3	0.293 ± 0.022	$3.839 \pm 0.037 \cdot 10^{-4}$	$4.49 \pm 0.78 \cdot 10^{-4}$	$2.490 \pm 0.010 \cdot 10^{-4}$	3.7732 ± 0.0064
i	err \tilde{V}_i^{tot}				
C	3287 ± 21	2.6922 ± 0.0061	$7.1 \pm 1.6 \cdot 10^{-5}$	3.0566 ± 0.0086	1.3474 ± 0.0039
K_1	2821 ± 19	2.696 ± 0.012	0.224 ± 0.045	7.665 ± 0.019	1.3684 ± 0.0030
K_2	145.6 ± 1.9	0.1754 ± 0.0016	0.162 ± 0.028	3.2002 ± 0.0087	0.09266 ± 0.00016
K_3	0.984 ± 0.033	$3.842 \pm 0.033 \cdot 10^{-4}$	$4.69 \pm 0.76 \cdot 10^{-4}$	0.56047 ± 0.00075	$2.498 \pm 0.012 \cdot 10^{-4}$
i	V_i				
P	15362 ± 42	6.033 ± 0.023	0.519 ± 0.081	8.514 ± 0.038	8.585 ± 0.016

Table 5.4: Estimates of mean square errors of final MC estimators of sensitivity indices of the SB model computed using grid-based method (Grid), schemes E using MC procedure (E) and hybrid approach (E-QMC) and schemes EMe and ETe in MC procedure. The errors are given along with their estimated standard deviations (see main text in Section 5.1 for details).

DM	Mean	AveVar	G σ	GFF	GCV
SB	230.069 ± 0.092	170.4 ± 1.0	13	0.74	0.057
MBMD	10.0361 ± 0.0099	7.012 ± 0.038	2.6	0.7	0.26
GTS	30.299 ± 0.060	368.4 ± 1.6	19	12	0.63

Table 5.5: Estimates of means and different measures of dispersion like mean variance (AveVar), generalized standard deviation ($G\sigma$), Fano Factor (GFF) (3.34) and coefficient of variation (GCV) (3.33) computed for SB, MBMD and GTS models in 50000 step MC procedures using scheme E and RTC algorithm.

5.3. Many births - many deaths model

Chemical reaction network of many births - many deaths (MBMD) model contains one species X and 5 different birth and death reactions can occur

$$\{R_{bi} : \emptyset \longrightarrow X, \quad R_{di} : X \longrightarrow \emptyset\}_{i \in I_5}.$$

These reactions are ordered as follows

$$\{R_i := R_{bi}, \quad R_{5+i} := R_{di}\}_{i \in I_5}. \quad (5.3)$$

The kinetic formulas of birth reactions are $a_{bi}(x) = K_{bi}$ and of death reactions $a_{di}(x) = K_{di}x$, where the distributions of kinetic rates are $K_{di} \sim U(0.010, 0.040)$ and $K_{bi} \sim U(0.10, 0.40)$ for $i \in I_5$. The initial number of particles C has distribution $U_d(5, 15)$ and we assume all parameters to be independent. The observable for which we count sensitivity indices is the number of particles of species X at time $t = 5$. The results of a 50000 step MC procedure computing sensitivity indices using RTC algorithm and scheme E are given in Table 5.8. In the next experiment we used three different constructions of DM to investigate variances of estimators of sensitivity indices using them. The first two are RTC and GD constructions applied to the model described above. The third is GD construction but applied to a reaction network with reordered indices

$$\{R_{2i-1} := R_{bi}, \quad R_{2i} := R_{di}\}_{i \in I_5}. \quad (5.4)$$

The idea behind such reordering was to facilitate switching between birth and death reactions in a given step of GD construction for different values of model parameters and thus

i	\tilde{V}_i	\tilde{V}_i^{tot}	\tilde{S}_i	\tilde{S}_i^{tot}
α_1	42.14 ± 0.55	43.33 ± 0.56	0.43	0.45
α_2	12.83 ± 0.40	13.80 ± 0.41	0.13	0.14
β	2.72 ± 0.16	2.73 ± 0.15	0.028	0.028
γ	37.74 ± 0.63	38.54 ± 0.64	0.39	0.4
i	V_i	V_i^{tot}	S_i	S_i^{tot}
P	96.96 ± 0.84	246.7 ± 1.0	0.21	0.53
R	218.6 ± 1.6	368.4 ± 1.6	0.47	0.79
P, R	465.3 ± 1.7	465.3 ± 1.7	1	1

Table 5.6: Estimates of sensitivity indices for TS model computed in a 50000 step MC procedure using RTC algorithm and scheme E.

i	E		EMe		ETe	
	GD	RTC	GD	RTC	GD	RTC
	\tilde{V}_i err					
α_1	16.05 ± 0.14	7.697 ± 0.086	13.820 ± 0.089	6.307 ± 0.053	85.42 ± 0.28	59.38 ± 0.26
α_2	5.350 ± 0.068	4.067 ± 0.050	5.098 ± 0.053	3.636 ± 0.034	46.38 ± 0.22	39.61 ± 0.18
β	3.118 ± 0.058	0.640 ± 0.022	2.960 ± 0.043	0.586 ± 0.016	35.02 ± 0.19	14.387 ± 0.100
γ	11.41 ± 0.11	9.950 ± 0.098	9.733 ± 0.074	7.635 ± 0.051	67.52 ± 0.28	60.52 ± 0.26
i	\tilde{V}_i^{tot} err					
α_1	16.27 ± 0.15	7.721 ± 0.085	60.39 ± 0.23	36.55 ± 0.14	13.755 ± 0.082	6.349 ± 0.058
α_2	5.720 ± 0.075	4.223 ± 0.052	39.96 ± 0.16	35.91 ± 0.14	5.463 ± 0.054	3.869 ± 0.036
β	3.311 ± 0.058	0.658 ± 0.025	34.22 ± 0.19	15.01 ± 0.11	3.188 ± 0.053	0.582 ± 0.019
γ	11.92 ± 0.11	10.315 ± 0.099	50.00 ± 0.18	46.25 ± 0.17	10.181 ± 0.070	7.942 ± 0.061
i	V_i err					
P	22.39 ± 0.14	17.46 ± 0.12	28.83 ± 0.15	19.87 ± 0.10	28.55 ± 0.14	19.93 ± 0.10
P, R	56.94 ± 0.21	68.88 ± 0.27	32.880 ± 0.097	38.28 ± 0.10	43.28 ± 0.13	45.95 ± 0.12

Table 5.7: Estimates of variances of final MC estimators of sensitivity indices for TS model computed using RTC and GD methods for different schemes. See main text in Section 5.2 for details.

to reduce the coupling of the observable to the noise term as discussed in Section 4.6. In Table 5.9 we compare variances of final MC estimators of some sensitivity indices, estimated from 10 independent runs of 5000 step MC procedures using scheme E and three different constructions of DM we described, similarly as in previous Sections. We can see that the estimates of variances of final MC estimators of main sensitivity indices with respect to parameters K_{b1} and K_{d1} estimated with RTC method are about two times lower than the ones estimated with GD method with initial order of indices and over 30 times lower for reordered indices. Note, however, that for main sensitivity indices of parameter C estimator using GD method with reordered reaction indices achieves slightly lower variance than the one with initial order of indices. When using GD method in scheme EM we received lower estimates of variance for initial order of indices rather than the reordered indices for all main sensitivity indices of individual parameters and similarly for scheme ET and total sensitivity indices (data not shown).

i	\tilde{V}_i	\tilde{V}_i^{tot}	\tilde{S}_i	\tilde{S}_i^{tot}
X	2.8966 ± 0.0038	2.9240 ± 0.0038	0.73	0.73
k_{b1}	0.10384 ± 0.00026	0.10407 ± 0.00026	0.026	0.026
k_{d1}	0.10476 ± 0.00025	0.11108 ± 0.00025	0.026	0.028
i	V_i	V_i^{tot}	S_i	S_i^{tot}
P	3.9792 ± 0.0061	6.0938 ± 0.0068	0.36	0.55
R	4.972 ± 0.020	7.087 ± 0.021	0.45	0.64
P, R	11.066 ± 0.021	11.066 ± 0.021	1	1

Table 5.8: Estimates of sensitivity indices for MBMD model computed in a 50000 step MC procedure using RTC algorithm and scheme E.

i	GDR	GDI	RTC
	$\delta\tilde{V}_i(10^{-6})$		
C	485.4 ± 2.9	528.6 ± 2.0	341.3 ± 1.3
k_{b1}	117.89 ± 0.60	6.871 ± 0.035	3.441 ± 0.014
k_{d1}	95.43 ± 0.36	5.282 ± 0.046	2.725 ± 0.030
i	$\delta V_i(10^{-6})$		
P	1054.3 ± 4.4	688.3 ± 3.3	632.5 ± 3.8
P, R	1356.1 ± 4.4	2104.0 ± 7.4	2091.3 ± 8.0

Table 5.9: Estimates of variances of final MC estimators using GD algorithm with reordered of indices (GDR) and GD and RTC methods with initial order of indices (denoted by GDI and RTC) for MBMD model. See main text in Section 5.3 for details.

Appendix A

Mathematical background

Unless stated otherwise we assume all measurable spaces to be standard Borel [26] and random variables to take values in such spaces, as well as all functions from one measurable space to another to be measurable [15]. We say that random variables are equal or uniquely determined if they are equal or uniquely almost surely (a.s.). For a measure space \mathcal{M} with measure μ by $L^p(\mu)$ we denote the space of classes of equivalence on the set of functions f from \mathcal{M} to \mathbb{R} , such that $\int |f|^p d\mu < \infty$ and $f \sim g$ iff $f = g$ a. s. μ (compare [50] Section 3.10), but as custom call these classes functions. For p, q natural, $p > q$ and μ finite it holds that from $f \in L^p(\mu)$ it follows $f \in L^q(\mu)$. Whenever dealing with random variables we assume some underlying probability space $(\Omega, \mathcal{F}, \mathbb{P})$ [15].

Definition 14. For two natural numbers $a \leq b$ we say that random variable X has uniform discrete distribution $U_d(a, b)$ if for any c natural such that $a \leq c \leq b$

$$P(X = c) = \frac{1}{b - a + 1}. \quad (\text{A.1})$$

Definition 15. The support[33] of a probability measure μ on the measure space $(\mathbb{R}^n, \mathcal{B}(\mathbb{R}^n))$ is defined as set $\{x \in \mathbb{R}^n : P(A) > 0 \text{ for every open rectangle } A \text{ containing } x\}$.

For $A \in \mathcal{F}$ we denote by $\mathbb{1}_A$ the indicator of the set A , that is $\mathbb{1}_A(\omega) = 1$ if $\omega \in A$ and 0 otherwise. Definition of the conditional expectation of a random variable $Y \in L^1(\mathbb{P})$ given X , which we denote $\mathbb{E}(Y|X)$ can be found in any standard probability text-book, like [15]. Conditional expectation is a random variable and is uniquely determined. We need the following well-known property of conditional expectation.

Theorem 16. For a function $f(X, Y) \in L(\mathbb{P})$ of independent random variables X, Y we have

$$\mathbb{E}(f(X, Y)|X) = (\mathbb{E}f(x, Y))_{x=X}. \quad (\text{A.2})$$

Conditional probability of an event $B \subset \Omega$ given random variable X is defined as

$$\mathbb{P}(B|X) := \mathbb{E}(\mathbb{1}_B|X). \quad (\text{A.3})$$

Below we give definition of conditional distribution ([6] chap. 20, def. 1).

Definition 17. For 2 random variables X and Y on $(\Omega, \mathcal{F}, \mathbb{P})$ and with values in (S_1, \mathcal{S}_1) and (S_2, \mathcal{S}_2) respectively, we call $\mu_{Y|X} : S_1 \times \mathcal{S}_2 \mapsto [0, 1]$ conditional distribution of Y given X if the following conditions are satisfied.

1. For every $x \in S_1$ $\mu_{Y|X}(x, \cdot)$ is a probability measure on \mathcal{S}_2 .
2. $\forall A \in \mathcal{S}_2$ function $x \mapsto \mu_{Y|X}(x, A)$ is measurable.
3. $\forall A \in \mathcal{S}_2$ $\mu_{Y|X}(X, A)$ is a version of $\mathbb{P}(Y \in A|X)$.

We also say that $\mu_{Y|X}(\cdot)$ is conditional distribution of Y given $X = x$.

It turns out that for random variables Y and X with values in standard Borel spaces such as $(\mathbb{R}^n, \mathcal{B}(\mathbb{R}^n))$ conditional distribution of Y given X exists and is in certain sense unique (see Chap. 1 in [26]). It holds [6] that for $g(Y) \in L^1(\mathbb{P})$ and any random variable $X \sim \mu_X$ if $\mu_{Y|X}$ exists we have

$$\mathbb{E}(g(Y)|X) = \int g(y) \mu_{Y|X}(X, dy). \quad (\text{A.4})$$

In particular, $\mathbb{E}(g(Y)|X)$ is certain function of X and its distribution is determined by μ_X and $\mu_{Y|X}(\cdot)$.

Theorem 18. *Using notations and assumptions from Section 2.2, if for every value $p = (c, k)$ of $P = (C, K)$ we have $h(p, R) \sim \mu_{DMCP}(RN(k), c)$, then $\mu_{DMCP}(RN(k), c)$ is conditional probability of $h(P, R)$ given $P = p$.*

Proof. Point 1 in definition 17 obviously holds, proof of point 2 is standard and the proof of point 3 is as follows

$$\begin{aligned} \forall_{A \in \mathcal{B}(E^T)} \mathbb{P}(h(P, R) \in A | P) &= \mathbb{P}(h(p, R) \in A)_{p=P} \\ &= \mu_{DMCP}(RN(K), C)(A), \end{aligned} \quad (\text{A.5})$$

where in the first equality we used (A.3) and Theorem 16. \square

Appendix B

Some further estimators and proof of relation between inefficiency constants

Use notations introduced when defining scheme E in Section 4.5, we define here sub schemes of E for estimation of main and total sensitivity indices with respect to pairs (P_i, P_j) . We first define helper estimator

$$\widehat{E^2}_{kl,E} := \frac{1}{8} \sum_{i=0}^1 \sum_{j=0}^1 (s_k[i][j]s_k[1-i][1-j] + s_l[i][j]s_l[1-i][1-j]). \quad (\text{B.1})$$

The estimator for $V_{(P_k, P_l)}$ is

$$\widehat{V}_{kl,E} := \frac{1}{4} \sum_{i=0}^1 \sum_{j=0}^1 (s_k[i][j]s_l[1-i][1-j]) - \widehat{E^2}_{kl,E}, \quad (\text{B.2})$$

while for $\tilde{V}_{(P_k, P_l)}^{tot}$ the estimator is

$$\widehat{\tilde{V}}_{kl,E}^{tot} := \frac{1}{8} \sum_{i=0}^1 \sum_{j=0}^1 (s_k[i][j]s_k[i][1-j] + s_l[i][j]s_l[i][1-j] - 2s_k[i][j]s_l[i][1-j]). \quad (\text{B.3})$$

The following lemma is needed for the proof of Theorem (13).

Lemma 19. *For a random vector $X = (X_i)_{i=1}^3$ with independent coordinates let $g(X) \in L^4(\mathbb{P})$ and let random variables $Y_i[j]$ for $i \in I_3$ and $j \in \{0, 1\}$ be mutually independent and fulfill $Y_i[j] \sim X_i$. We denote, for $i, j, k \in \{0, 1\}$*

$$g[i][j][k] = g(Y_1[i], Y_2[j], Y_3[k]). \quad (\text{B.4})$$

For $i \in \{0, 1\}$ we denote $B[i] = g[1-i][i][0] - g[i][i][0]$, $C[i] = g[1-i][1-i][1] - g[i][1-i][1]$ and

$$A[i] = B[i]C[i]. \quad (\text{B.5})$$

It holds

$$\text{Cov}(A[0], A[1]) \geq 0. \quad (\text{B.6})$$

Proof. Let us denote by $(V_J)_{J \subset I}$ the elements of ANOVA decomposition of variance of $g(X_1, X_2, X_3)$ (see section 3.1). From Theorem 6 for every $i \in \{0, 1\}$ $\mathbb{E}(A[i]) = 2V_1$. Thus we can write

$$\text{Cov}(A[0], A[1]) = \mathbb{E}(B[0]B[1]C[0]C[1]) - 4V_1^2. \quad (\text{B.7})$$

Since $B[0]B[1] \sim C[0]C[1]$ it holds

$$\mathbb{E}(B[0]B[1]C[0]C[1]) = \text{Cov}(B[0]B[1], C[0]C[1]) + \mathbb{E}^2(B[0]B[1]). \quad (\text{B.8})$$

From Theorem 6 covariance on the rhs of (B.8) fulfills

$$\begin{aligned} \text{Cov}(B[0]B[1], C[0]C[1]) &= \text{Cov}((g[1][0][0] - g[0][0][0])(g[0][1][0] - g[1][1][0]), \\ &\quad (g[1][0][1] - g[0][0][1])(g[0][1][1] - g[1][1][1])) \\ &= \text{Var}(\mathbb{E}((g[1][0][0] - g[0][0][0])(g[0][1][0] - g[1][1][0])|Y_1, Y_2)) \\ &= \text{Var}(\mathbb{E}(B[0]B[1]|Y_1, Y_2)). \end{aligned} \quad (\text{B.9})$$

We also have

$$\begin{aligned} \mathbb{E}(B[0]B[1]) &= \mathbb{E}((g[1][0][0] - g[0][0][0])(g[0][1][0] - g[1][1][0])) \\ &= 2\mathbb{E}(\mathbb{E}^2(g[0][0][0]|Y_3) - \mathbb{E}^2(g[1][0][0]|Y_1, Y_3)) = -2(V_1 + V_{1,3}). \end{aligned} \quad (\text{B.10})$$

Combining (B.7), (B.8), (B.9) and (B.10) we receive

$$\text{Cov}(A[0], A[1]) = \text{Var}(\mathbb{E}(B[0]B[1]|Y_1, Y_2)) + 4V_{1,3}(2V_1 + V_{1,3}) \geq 0. \quad (\text{B.11})$$

□

Below we provide the proof of Theorem 13.

Proof. For $i \in \{0, 1\}$ let us denote

$$A[i] = (\tilde{s}_k[i][0] - \tilde{s}[i][0])(\tilde{s}[1-i][1] - \tilde{s}_k[1-i][1]) \quad (\text{B.12})$$

and k_i the number of function evaluations used by scheme i . Using our standard notation for observables of estimators we have

$$k_E \text{Var}(V_{i,E}) = k_{EM}(\text{Var}(V_{i,EM}) + \text{Cov}(A[0], A[1])). \quad (\text{B.13})$$

For $X_1 = P_k$, $X_2 = P_{\sim k}$, $X_3 = R$, function g such that $g(X_1, X_2, X_3) = f(P, R)$ and $g[i][j][k]$ defined as in Lemma 19, we have $(\tilde{s}_k[i][j], \tilde{s}[i][j]) \sim (g[1-i][i][j], g[i][i][j])$ for $i, j \in \{0, 1\}$. In particular $A[i]$ for $i \in \{0, 1\}$ given by (B.12) and defined in Lemma 19 have the same joint distribution, thus here we also have

$$\text{Cov}(A[0], A[1]) \geq 0. \quad (\text{B.14})$$

Expression (4.83) now follows from (B.13), (B.14) and Theorem 10. □

Appendix C

More efficient estimators for 3 parameters

Schemes for estimation of sensitivity indices of functions and their conditional expectations can be improved for the number of parameters N_P equal to 3, so that the new schemes allow for estimation of the same main and total sensitivity indices with respect to individual parameters, but with lower or equal inefficiency constants, in which equality holds only if both constants are equal to 0. For certain index $k \in I_3$ one may resign from using s_k . The new estimates of the indices associated with k -th parameter are computed using values of observables $(\tilde{P}_{(k)}[i])_{i=0}^1$ in place of $(\tilde{P}[i])_{i=0}^1$ in estimator for computing k -th index. This does not change the expected value or variance of the estimator but allows for using $((s_l[i][j], s_m[1-i][j])_{i=0}^1)_{j=0}^1$ in place of $((s[i][j], s_k[1-i][j])_{i=0}^1)_{j=0}^1$ in sub scheme computing k -th indices in scheme E or $(s_l[i], s_m[1-i])_{i=0}^1$ in place of $(s[i], s_k[1-i])_{i=0}^1$ in such sub scheme of O . This reduces the number of function evaluations needed by a scheme by factor $\frac{3}{4}$, without changing the variance of its estimators. For instance the estimator for k -th main sensitivity index for output of such new scheme O3l created from O becomes

$$\hat{V}_{k,O3k} := \frac{1}{2}(s_l[0] - s_m[1])(s_m[0] - s_l[1]), \quad (\text{C.1})$$

while for the total index of output

$$\hat{V}_{k,O3k}^{tot} := \frac{1}{4} \sum_{i=0}^1 (s_l[i] - s_m[1-i])^2. \quad (\text{C.2})$$

For scheme E3l created in this way from E we have

$$\hat{V}_{l,E3k} := \frac{1}{4} \sum_{i=0}^1 (s_l[i][0] - s_m[1-i][0])(s_m[1-i][1] - s_l[1-i][1]) \quad (\text{C.3})$$

and

$$\hat{\tilde{V}}_{l,E3k}^{tot} := \frac{1}{4} \sum_{i=0}^1 (s_l[i][0] - s_m[1-i][0])(s_l[i][1] - s_m[1-i][1]). \quad (\text{C.4})$$

Alternatively, instead of resigning from using s_k one can apply it to compute analogous new estimators for l and m and use for all indices the averages of old and new estimators. Thanks to theorem 11 variances of such estimators are smaller or equal to the variances of original estimators.

Appendix D

Sensitivity indices for simple birth model

Instead of one birth process with rate equal to the sum of coordinates of random vector $K = (K_i)_{i=1}^3$ let us consider a model consisting of three birth processes with rates equal to its consecutive coordinates. This does not change conditional distribution of the process given the parameters, as in both cases it is the distribution of sum of three independent Poisson processes with given rates. In particular such change does not influence the values of variance-based sensitivity indices we compute here. We use a construction of such process resulting from integral equation (1.8) generalized to random parameters

$$Y_t = C + \sum_{i=1}^3 N_i(K_i t). \quad (\text{D.1})$$

Using formula

$$\sum_{i=1}^n i^3 = \frac{n(n+1)(2n+1)}{6} \quad (\text{D.2})$$

we receive for $X \sim U_d(a, b)$ (see Definition 14)

$$\text{Var}(X) = \frac{b(b+1)(2b+1) - (a-1)a(2a-1)}{6(b-a+1)} - \left(\frac{a+b}{2}\right)^2. \quad (\text{D.3})$$

From the last expression we have

$$V_C = \text{Var}(\mathbb{E}(Y_t|C)) = \text{Var}(C) = 310. \quad (\text{D.4})$$

Denoting $\text{Pois}(\lambda)$ Poisson distribution with parameter λ , for any Poisson process N it holds $N(\lambda) \sim \text{Pois}(\lambda)$. In particular

$$\mathbb{E}(N(\lambda)) = \lambda \quad (\text{D.5})$$

and

$$\mathbb{E}(N(\lambda)^2) = \lambda^2 + \lambda. \quad (\text{D.6})$$

From Theorem 16 we receive for $i \in I_3$

$$\mathbb{E}(N_i(K_i t)|K_i) = (\mathbb{E}(N_i(k_i t)))_{k_i=K_i} = K_i t. \quad (\text{D.7})$$

Since for $X \sim U(a, b)$ we have

$$\text{Var}(X) = \frac{(b-a)^2}{12}, \quad (\text{D.8})$$

we obtain

$$V_{K_1} = \text{Var}(K_1 t) = 300, \quad (\text{D.9})$$

and similarly $V_{K_2} = 75$ and $V_{K_3} = 3$. From independence of summands in

$$\mathbb{E}(Y_t|P) = \sum_{i=1}^3 K_i t + C \quad (\text{D.10})$$

we receive

$$V_P = V_C + \sum_{i=1}^3 V_{K_i} = 688 \quad (\text{D.11})$$

and $\tilde{V}_i^{tot} = V_i$ for every i -th parameter. From (D.6) we receive for $i \in I_3$

$$\mathbb{E}(N(K_i t)^2) = \mathbb{E}((\mathbb{E}(N(k_i t)^2))_{k_i=K_i}) = \mathbb{E}(K_i^2)t^2 + \mathbb{E}(K_i)t, \quad (\text{D.12})$$

while using further (D.9) and (D.12)

$$\text{Var}(N(K_i t)) = \mathbb{E}(N(K_i t)^2) - \mathbb{E}^2(N(K_i t)) = V_{K_i} + \mathbb{E}(K_i)t. \quad (\text{D.13})$$

From (D.13) and independence of summands in the rhs of (D.1) we receive

$$\begin{aligned} D &= \text{Var}(Y_t) = V_C + \sum_{i=1}^3 (V_{K_i} + \mathbb{E}(K_i)t) \\ &= V_P + \mathbb{E}\left(\sum_{i=1}^3 K_i\right)t = 858. \end{aligned} \quad (\text{D.14})$$

We also have

$$V_R^{tot} = D - V_P = 170. \quad (\text{D.15})$$

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