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Review

A comparison of deterministic and stochastic approaches for sensitivity analysis in computational systems biology

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Abstract

With the recent rising application of mathematical models in the field of computational systems biology, the interest in sensitivity analysis methods had increased. The stochastic approach, based on chemical master equations (CMEs), and the deterministic approach, based on ordinary differential equations (ODEs), are the two main approaches for analysing mathematical models of biochemical systems. In this work, the performance of these approaches to compute sensitivity coefficients is explored in situations where stochastic and deterministic simulation can potentially provide different results (systems with unstable steady states, oscillators with population extinction and bistable systems). We consider two methods in the deterministic approach, namely the direct differential method and the finite difference (FD) method, and five methods in the stochastic approach, namely the Girsanov transformation (GT), the independent random number (IRN) method, the common random number (CRN) method, the coupled finite difference (CFD) method and the rejection-based finite difference (RFD) method. The reviewed methods are compared in terms of sensitivity values and computational time to identify differences in outcome that can highlight conditions in which one approach performs better than the other.

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1 Introduction

Computational systems biology is emerging as a fundamental tool for life-science research, which aims at developing *models* representing biological phenomena and reliable *computational techniques* for their simulation and analysis [1; 2; 3; 4; 5]. *Sensitivity analysis* is the study of how the uncertainty in the output of a mathematical model can be apportioned to different sources of uncertainty in its inputs. When the mathematical model represents a biological system, the results of sensitivity analysis can be used to (i) test the robustness of model results in presence of experimental data uncertainty; (ii) increase our understanding of the relationships between input and output variables by identifying molecules playing a leading role in the development of a modeled phenotype or disease (e.g. biomarkers, drug targets, etc.); (iii) simplify the model by fixing inputs that have no effect on the output or by omitting reaction subnetworks that are not sensitive to the data used to calibrate the model (model reduction). The rising importance of sensitivity analysis is also demonstrated by the increasing publication rate of papers dealing with this topic. Starting from about 200 papers published before 1990, the number of papers available in PubMed are exponentially increasing: 1,064 in the decade 1990–1999, 4,071 in the decade 2000-2009 and more than 10,000 papers published in the period 2010–2018.

Since sensitivity analysis is often computed by repeated model simulations, a well known issue is the high computational effort required to complete the analysis. The computational overhead increases when an accurate stochastic simulation strategy is considered with respect to classical deterministic techniques. The increase of computational power should be compensated by the increased result accuracy. However, it is often hard to understand in advance which is the best approach to apply, since deterministic sensitivity analysis can be adequate to assess the reliability of model results and very often is much faster than any stochastic approach. After about one decade from the publication in this journal of a review comparing stochastic versus deterministic simulation approaches [4], this contribution moves one step further by comparing stochastic and deterministic algorithms for sensitivity analysis. Among the different methodologies for sensitivity analysis, we herein consider local sensitivity analysis where one-factor-at-a-time (OFAT or OAT) is perturbed. We do this, because these methodologies are the ones mostly used in the modeling literature since the computation of sensitivity coefficients due to the simultaneous perturbation of many parameter rates requires, especially in the stochastic approach, an exponentially increase of the computational effort. The reviewed methodologies are tested by considering models described both as stochastic biochemical reactions and as set of mass action ODEs to identify differences in outcome that can highlight challenging conditions in which one approach performs better than the other, including systems with unstable steady states, oscillators with population extinction, bistable systems. In the following, three *ad hoc* models have been chosen as case studies for each of these conditions.

1.1 Mathematical framework

Hereafter we will consider well-stirred biochemical reaction systems consisting of n chemical species $S_1, ..., S_n$ interacting through m reactions $R_1, ..., R_m$ in a well-mixed environment, where position and speed of molecular species are randomized and therefore they do not affect reaction executions. A particular reaction R_j has the general scheme

$$v_{j1}^{-}S_1 + ... + v_{jn}^{-}S_n \xrightarrow{c_j} v_{j1}^{+}S_1 + ... + v_{jn}^{+}S_n, \tag{1}$$

where the species on the left of the arrow are called *reactants*, while the ones on the right are *products*. The non-negative integers v_{ji}^{-} and v_{ji}^{+} are the *stoichiometric coefficients* indicating how many molecules of reactant and product are involved. The overall change in species population by R_j is represented by the *state change vector* $\mathbf{v}_j$, where its ith component is equal to $v_{ji}^{+} - v_{ji}^{-}$. The label c_j on the arrow is the *stochastic reaction constant* as introduced by Gillespie [6]. The state of the system at time t is represented by a vector $\mathbf{X}(t) = (X_1(t), ..., X_n(t))$, where $X_i(t)$ is the number of molecules of species S_i in the system at time t.

The probability that reaction R_j fires in the next infinitesimal time $t + dt$, given the state $\mathbf{X}(t)$ at time t, is $a_j(\mathbf{X}(t))dt$, where the *propensity function* a_j can be computed as a function of the reaction constant c_j and the state $\mathbf{X}(t)$. In case of mass action kinetics [6; 7], the propensity is defined as

$$a_j(\mathbf{X}(t)) = c_j h_j(\mathbf{X}(t)), \tag{2}$$

where $h_j(\mathbf{X}(t))$ counts the number of distinct combinations of reactants through the following formula

$$h_j(\mathbf{X}(t)) = \prod_i \binom{X_i(t)}{v_{ji}^{-}}. \tag{3}$$

An exact realization of $\mathbf{X}(t)$ can be obtained by applying the stochastic simulation algorithm (SSA), which is based on an event-driven simulation approach where reactions are randomly selected to fire according to their propensity. Several implementations of SSA have been proposed, including the direct method (DM) [6; 7], the next reaction method (NRM) [8] and the rejection-based SSA (RSSA) [9]. We refer to [5; 4] for a comprehensive review of stochastic simulation algorithms.

When the number of molecules of each modeled species is large enough for being safely approximated by concentrations that vary continuously (continuum hypothesis [5]), then the reaction system can be translated into a set of ODEs by relying on the law of mass action. This allows moving from a stochastic to a deterministic approach, where the intrinsic randomness of the system is not anymore considered. In the deterministic framework, the state of the system at time t is represented by the vector of concentrations $[\mathbf{X}](t) = ([X_1](t), ..., [X_n](t))$, where $[X_i](t)$ is the concentration of species S_i in the system at time t. The molar concentration $[X_i](t)$ of species S_i is defined as

$$[X_i](t) = \frac{X_i(t)}{N_A V} \tag{4}$$

where V is the reaction volume and N_A is the Avogadro's number. Consider Eq.(1), the corresponding ODE representing the evolution of species S_i is

$$\frac{d[X_i](t)}{dt} = \sum_{j=1}^{m}(d_j \mathbf{v}_{ji} \prod_{l=1}^{n}[X_l]^{\mathbf{v}_{jl}^{-}}(t)) \quad i = 1, ..., n, \tag{5}$$

where d_j is the *deterministic rate* of reaction R_j, which can be easily obtained by converting the stochastic rate c_j [5]. A system of ODEs can be represented in a compact matrix form as:

$$\frac{d[\mathbf{X}](t)}{dt} = \mathbf{F}([\mathbf{X}], \mathbf{d}, t), \tag{6}$$

where $\mathbf{F} : \mathbb{R}^n \times \mathbb{R}^m \times \mathbb{R} \rightarrow \mathbb{R}^n$ is the vector of n functions F_i providing the time derivatives of the species concentrations. The simulation of a system of ODEs is addressed by solving the *initial-value problem*, which corresponds to solve Eq.(6) given the initial concentration of modeled species. Since the number and complexity of the ODEs is often too high to allow an analytical solution, several numerical methods have been introduced to approximate the behaviour in time of the model. A comprehensive collection of numerical methods for deterministic simulation is presented in [10; 5].

2 Computational methods for sensitivity analysis

Sensitivity analysis is herein defined as the first-order partial derivatives of the system output with respect to the reaction rates. In the context of stochastic chemical kinetics, let $\mathbf{X}^{\mathbf{c}}(t)$ be the state of the system at time t computed by considering the vector $\mathbf{c} = (c_1, ..., c_m)$ of stochastic reaction rates. The quantity $Q(\mathbf{c})$ providing the dependence of the state on $\mathbf{c}$ is:

$$Q(\mathbf{c}) = \mathbb{E}[\mathbf{X}^{\mathbf{c}}(t)], \tag{7}$$

where $\mathbb{E}[-]$ denotes the expectation operator. We note that in Eq.(7), $Q(\mathbf{c})$ measures the direct dependence of the state on the rate vector $\mathbf{c}$, but it is easy to generalize the sensitivity measurement by applying a function f of interest on the state such that $Q(\mathbf{c}) = \mathbb{E}[f(\mathbf{X}^{\mathbf{c}}(t))]$. Let θ be the reaction index for which we want to measure the sensitivity, the aim of stochastic sensitivity analysis is to efficiently compute the sensitivity coefficient

$$\mathbf{S}_\theta(t) = \frac{\partial Q(\mathbf{c})}{\partial c_\theta} = \frac{\partial \mathbb{E}[\mathbf{X}^{\mathbf{c}}(t)]}{\partial c_\theta} \tag{8}$$

using stochastic simulation. The corresponding sensitivity coefficient in the deterministic approach is defined as:

$$\mathbf{S}_\theta(t) = \frac{\partial [\mathbf{X}]^{\mathbf{d}}(t)}{\partial d_\theta}, \tag{9}$$

where $[\mathbf{X}]^{\mathbf{d}}(t)$ is the state of the system at time t computed by considering the vector $\mathbf{d} = (d_1, ..., d_m)$ of reaction deterministic rates.

2.1 Stochastic sensitivity analysis

In this section, we present different methods to construct an estimator for the sensitivity coefficient $\mathbf{S}_\theta(t)$ defined in Eq.(8). These approaches are different in their bias and variance and can be classified into two categories: *infinitesimal perturbation estimators* and *finite perturbation estimators* [11]. An infinitesimal perturbation estimator derives the sensitivity coefficients by using information from the simulation of the system with nominal rates $\mathbf{c}$. Instead, a finite perturbation estimator perturbs the nominal rates of the system by a small amount, hence introducing bias into the estimation, depending on the finite discretization scheme. In the following, we will consider the *Girsanov transformation (GT) method* [12], which provides an efficient implementation of the infinitesimal perturbation estimator, while for the finite perturbation methods we will consider the *independent random number (IRN) method*, the *common random number (CRN) method* [13], the *coupled finite difference (CFD) method* [14] and the *rejection-based finite difference (RFD) method* [15]. For the sake of simplicity, we provide here only a general explanation of the considered algorithms. A more detailed explanation and the complete pseudocode implementations are provided in Supplementary Material. Further improvements of the considered strategies are also discussed in [16; 17; 18; 19; 20; 21; 22].

The principle of the GT method is to rewrite the derivative of the expectation in such a way that it can be directly computed from the simulation. Specifically, the sensitivity coefficient $\mathbf{S}_\theta$ in Eq.(8) can be rewritten by means of probability measure transformation [23] as

$$\mathbf{S}_\theta(t) = \mathbb{E}\Big[\mathbf{X}^{\mathbf{c}}(t) w_\theta(\mathbf{X}^{\mathbf{c}}(t))\Big], \tag{10}$$

where $w_\theta(\mathbf{X}^{\mathbf{c}}(t))$ is the weight function defined as

$$w_\theta(\mathbf{X}^{\mathbf{c}}(t)) = \sum_{l=1}^{L} w_{\theta,l}(\mathbf{X}^{\mathbf{c}}(t_l)). \tag{11}$$

In the previous equation, L gives the number of reaction events occurring at time $0 < t_1 < \cdots < t_L = t$, where the lth event is denoted by a pair (μ_l, τ_l) such that μ_l is the reaction firing index and $\tau_l = t_{l+1} - t_l$ is the waiting time to the firing. Each term of the sum in Eq.(11) is computed as

$$w_{\theta,l}(\mathbf{X}^{\mathbf{c}}(t_l)) = \frac{\partial \ln a_\theta(\mathbf{X}^{\mathbf{c}}(t_l))}{\partial c_\theta}\Big(I_\theta(\mu_l) - a_\theta(\mathbf{X}^{\mathbf{c}}(t_l))\tau_l\Big) \tag{12}$$

with

$$I_\theta(\mu_l) = \begin{cases} 1, & \text{if } \mu_l = \theta \\ 0, & otherwise. \end{cases} \tag{13}$$

Eq.(10) gives the mathematical basis of the GT method for computing an unbiased estimator of the sensitivity coefficient $\mathbf{S}_\theta$. It shows that $\mathbf{S}_\theta$ can be realized by simulating the process $\mathbf{X}^{\mathbf{c}}(t)$ until time t and then weighting the output by $w_\theta(\mathbf{X}^{\mathbf{c}}(t))$. Specifically, let K be the number of simulation runs and let $\mathbf{X}^{\mathbf{c}}_{[k]}(t)$ be a realization of the state $\mathbf{X}^{\mathbf{c}}(t)$ in the kth simulation run with $k = 1, \ldots, K$. The sensitivity coefficient $\mathbf{S}_\theta$ in Eq.(10) can be estimated as

$$\mathbf{S}_\theta(t) \approx \frac{1}{K}\sum_{k=1}^{K} \mathbf{X}^{\mathbf{c}}_{[k]}(t) w_\theta(\mathbf{X}^{\mathbf{c}}_{[k]}(t)). \tag{14}$$

The finite difference (FD) approach constitutes an alternative for computing the sensitivity coefficient $\mathbf{S}_\theta$. It directly estimates $\mathbf{S}_\theta$ by applying a small, but finite, perturbation amount to the nominal rate values. Specifically, let $\mathbf{e}_\theta$ be a unit m-vector in which the θth element is 1, while other elements are zeros. Let ϵ be a small scalar value and $\epsilon_\theta = \epsilon c_\theta$. The sensitivity coefficient $\mathbf{S}_\theta$ with respect to a reaction rate c_θ in Eq.(8) can be approximated by the *centered finite difference*:

$$\begin{aligned} \mathbf{S}_\theta(t) = \frac{\partial Q(\mathbf{c})}{\partial c_\theta} &\approx \frac{Q(\mathbf{c} + \epsilon_\theta \mathbf{e}_\theta) - Q(\mathbf{c} - \epsilon_\theta \mathbf{e}_\theta)}{2\epsilon_\theta} \\ &\approx \frac{\mathbb{E}[\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}(t)] - \mathbb{E}[\mathbf{X}^{\mathbf{c}-\epsilon_\theta \mathbf{e}_\theta}(t)]}{2\epsilon_\theta}, \end{aligned} \tag{15}$$

where $\mathbf{c}$ are the nominal rates and $\mathbf{c} \pm \epsilon_\theta \mathbf{e}_\theta$ are the perturbed ones. It can be shown by the Taylor series expansion that the bias due to truncation error of the centered difference is $O(\epsilon_\theta^2)$. The sensitivity coefficient $\mathbf{S}_\theta$ in Eq.(15) can be constructed as

$$\mathbf{S}_\theta(t) = \frac{1}{K}\sum_{k=1}^{K} \frac{\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}_{[k]}(t) - \mathbf{X}^{\mathbf{c}-\epsilon_\theta \mathbf{e}_\theta}_{[k]}(t)}{2\epsilon_\theta}, \tag{16}$$

where K is the number of simulation runs, and $\mathbf{X}^{\mathbf{c}-\epsilon_\theta \mathbf{e}_\theta}_{[k]}$ and $\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}_{[k]}$ are the realizations of states with perturbed rates in the kth run, with $k = 1, \ldots K$, respectively.

The simplest method for implementing the FD estimator $\mathbf{S}_\theta$ in Eq.(15) is the IRN where two independent simulation runs are used to realize the states $\mathbf{X}^{\mathbf{c}-\epsilon_\theta \mathbf{e}_\theta}$ and $\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}$. The estimation by the IRN method, however, often has a large variance. The CRN [13] tries to reduce the variance of the estimator by using the same stream of random numbers for the realizations of these states. The idea behind this strategy is to induce a (positive) correlation between $\mathbf{X}^{\mathbf{c}-\epsilon_\theta \mathbf{e}_\theta}(t)$ and $\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}(t)$ so that the variance of the sensitivity coefficient $\mathbf{S}_\theta$ can be reduced by also increasing its efficiency. Although CRN can reduce the variance of $\mathbf{S}_\theta$, the induced correlation will be lost for long simulation time.

The CFD [14] and the RFD [15] have been recently introduced for further reducing the variance of the FD estimator $\mathbf{S}_\theta$ in Eq.(15). The foundation of these approaches is the decomposition of the Poisson processes, which represent the number of firings of reactions in the random time-change (RTC) representation, such that common Poisson processes are shared during the simulations of $\mathbf{X}^{\mathbf{c}-\epsilon_\theta \mathbf{e}_\theta}$ and $\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}$. To be more concrete, let $Po_{j,1}\Big(\int_0^t a_j(\mathbf{X}^{\mathbf{c}-\epsilon_\theta \mathbf{e}_\theta}(s))ds\Big)$ and $Po_{j,2}\Big(\int_0^t a_j(\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}(s))ds\Big)$, with $j = 1, \ldots, m$, be the Poisson processes representing the number of firings of reaction R_j in simulating $\mathbf{X}^{\mathbf{c}-\epsilon_\theta \mathbf{e}_\theta}(t)$ and $\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}(t)$, respectively. CFD decomposes these processes as

$$\begin{aligned} Po_{j,1}\Big(\int_0^t a_j(\mathbf{X}^{\mathbf{c}-\epsilon_\theta \mathbf{e}_\theta}(s))ds\Big) &= Po_j\Big(\int_0^t b_j(s)ds\Big) \\ &+ Po_{j,3}\Big(\int_0^t (a_j(\mathbf{X}^{\mathbf{c}-\epsilon_\theta \mathbf{e}_\theta}(s)) - b_j(s))ds\Big) \end{aligned} \tag{17}$$

and

$$\begin{aligned} Po_{j,2}\Big(\int_0^t a_j(\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}(s))ds\Big) &= Po_j\Big(\int_0^t b_j(s)ds\Big) \\ &+ Po_{j,4}\Big(\int_0^t (a_j(\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}(s)) - b_j(s))ds\Big), \end{aligned} \tag{18}$$

where $b_j(s) = \min(a_j(\mathbf{X}^{\mathbf{c}-\epsilon_\theta \mathbf{e}_\theta}(s)), a_j(\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}(s))$ for all $s \in [0, t]$. Thus, by sharing the common Poisson processes $Po_j(\int_0^t b_j(s)ds)$, with $j = 1, \ldots, m$ during the simulation, the variance of CFD estimator is reduced to be proportional to the variance of the residual Poisson processes $Po_{j,3}(\int_0^t (a_j(\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}(s)) - b_j(s))ds)$ and $Po_{j,4}(\int_0^t (a_j(\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}(s)) - b_j(s))ds)$.

RFD further reduces the variance of the estimator by decomposing the Poisson processes employing the idea of propensity upper bounds. Let $\overline{a}_j$ be an arbitrary propensity upper bound such that $\overline{a}_j \geq a_j(\mathbf{X}^{\mathbf{c}-\epsilon_\theta \mathbf{e}_\theta}(s))$ and $a_j(\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}(s))$ for all $s \in [0,t]$. We have

$$Po_{j,1}\Big(\int_0^t a_j(\mathbf{X}^{\mathbf{c}-\epsilon_\theta \mathbf{e}_\theta}(s))ds\Big) = Po_j\Big(\overline{a}_j t\Big) - Po_{j,3}\Big(\overline{a}_j t - \int_0^t a_j(\mathbf{X}^{\mathbf{c}-\epsilon_\theta \mathbf{e}_\theta}(s))ds\Big) \quad (19)$$

and

$$Po_{j,2}\Big(\int_0^t a_j(\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}(s))ds\Big) = Po_j\Big(\overline{a}_j t\Big) - Po_{j,4}\Big(\overline{a}_j t - \int_0^t a_j(\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}(s))ds\Big). \quad (20)$$

Based on the decompositions in Eqs.(19) and (20), RFD correlates the simulation of $\mathbf{X}^{\mathbf{c}-\epsilon_\theta \mathbf{e}_\theta}$ and $\mathbf{X}^{\mathbf{c}+\epsilon_\theta \mathbf{e}_\theta}$ by simulating the common Poisson process $Po_j(\overline{a}_j t)$ and then filtering out the selection by the corresponding exact propensities, exploiting the rejection-based simulation framework [9]. The variance of the estimator by RFD is reduced to be proportional to the variance of the residual Poisson process with rates equal to the difference between the upper bound and the exact propensity.

2.2 Deterministic sensitivity analysis

In this section, we present two popular methods to compute sensitivity analysis in the deterministic framework. These methods, namely the direct differential method and the finite difference method, are different in the level of approximation introduced to compute the sensitivity coefficient defined in Eq.(9). An exhaustive review of methods for deterministic sensitivity analysis of biological systems can be found in [24].

2.2.1 Direct differential method

One way to compute the sensitivity coefficients at different time points is through the direct differential method [25]. This method is a non-approximative technique in the sense that, given that the finite precision arithmetic of the computer is not taken into account, the values of the computed derivatives are exact. Consider Eq.(9), the corresponding set of n ODEs for the sensitivity coefficients is defined, for each reaction index $\theta = 1, ..., m$, as

$$\frac{d\mathbf{S}_\theta(t)}{dt} = \mathbf{F}_{d_\theta}(t) + \mathbf{J}(t) \times \mathbf{S}_\theta(t), \quad (21)$$

where $\mathbf{J}(t)$ is the Jacobian matrix of the original ODE system given by Eq.(6) and $\mathbf{F}_{d_\theta}(t)$ gives the vector of derivatives of each function $F_i(t)$ with respect to parameter d_θ. We recall that the Jacobian matrix is an $n \times n$ matrix in which the (i,j) element is given by $\partial F_i / \partial [X_j]$. A complete mathematical description on how to derive Eq.(21) can be found in the Supplementary Material. The sensitivity set of ODEs in Eq.(21) must be solved simultaneously with the original ODE system in Eq.(6) by means of a suitable numerical method. The initial condition for the first $n \times m$ variables of the complete model is 0, unless $d_\theta = [X_i](0)$. In the latter case the initial condition is 1.

The main disadvantage of the direct differential method is that it relies on the definition of the Jacobian matrix, which may require human intervention and it is time-consuming especially for large-scale or nonlinear problems. To overcome the problem, the temporal evolution of the sensitivity coefficients can be numerically estimated by the FD approximation.

2.2.2 Finite difference approximation

The principle of the FD approximation is that it approximates the differential operator by replacing the derivatives with the differential quotients. The approximation error between the numerical solution and the exact solution is determined by the error that is committed by moving from a differential operator to a difference operator. According to the error order, a FD method can be divided in first or second order. A commonly used second order FD method is the central difference approximation, which computes the sensitivity coefficient as:

$$\mathbf{S}_\theta(t) = \frac{\partial [\mathbf{X}](t)}{\partial d_\theta} \cong \frac{[\mathbf{X}]^{\mathbf{d}+\epsilon_\theta \mathbf{e}_\theta}(t) - [\mathbf{X}]^{\mathbf{d}-\epsilon_\theta \mathbf{e}_\theta}(t)}{2\epsilon_\theta}, \quad (22)$$

where ϵ_θ indicates the multiplication between the considered perturbation factor ϵ and the deterministic rate d_θ, and $\mathbf{e}_\theta$ is the unit m-vector as defined for the stochastic case. This method is easy to implement because it requires no extra code beyond the original model solver. The approximation error of the central FD approximation in Eq.(22) is $O(\epsilon^2)$.

3 Method comparison

In this section, the methods introduced in Sect.2 will be compared to identify potential differences in their output. Three theoretical models have been considered to test the computational approaches in specific conditions where stochastic and deterministic simulation provide different results. Such conditions are: systems with unstable steady states (described in Sect.3.1 by considering the Oregonator model [26]), oscillators with population extinction (described in Sect.3.2 by considering the Oscillator model [27]) and bistable systems (described in Sect.3.3 by considering the Schlögl model [31]). Since these conditions rely on important properties of dynamical systems, which are *per se* quite difficult to understand, we intentionally considered simple theoretical models, because our aim is to highlight result differences in very controlled situations. We think that this strategy has several benefits because it permits focusing on the investigated dynamical properties without being confused by the complexity of the model itself. On the other hand, the theoretical basis of these models may prevent a clear understanding of reaction stoichiometry from a chemical point of view. We refer to the provided references for any further detail on this topic.

For all benchmarks, four levels of comparison have been studied: (i) between the two deterministic methods, (ii) between the five stochastic methods, (iii) between stochastic and deterministic FD methods and (iv) between stochastic and deterministic "exact" methods (namely the direct differential method and the GT method). To provide a concise method comparison, all the sensitivity results provided in the following are related to one model parameter and one model variable. However, the results for the other model parameters and variables can be found in the Supplementary Material.

All calculations have been run in similar conditions on a Windows Server 2008 R2 computer, with 2 quad core Intel Xeon 2.13GHz CPUs and 20 GB of RAM memory. Deterministic simulations have been computed in MATLAB v.R2017b by means of the ODE solver *ode45*, while stochastic simulations have been computed by means of *ad hoc* implementations of the required methodologies. For all the stochastic algorithms, $10,000$ model simulations have been computed to derive the sensitivity coefficients. For FD methods, both in the deterministic and in the stochastic framework, we set the perturbation multiplicative factor $\epsilon = 0.01$. Finally, to allow a simple model translation between the deterministic and the stochastic framework, we assumed in all cases a theoretical reaction volume equal to the inverse of the Avogadro's number. This allows the semplification of Eq.(4) to have molar concentrations equal to abundances. For the sake of simplicity, we also omitted all unit of

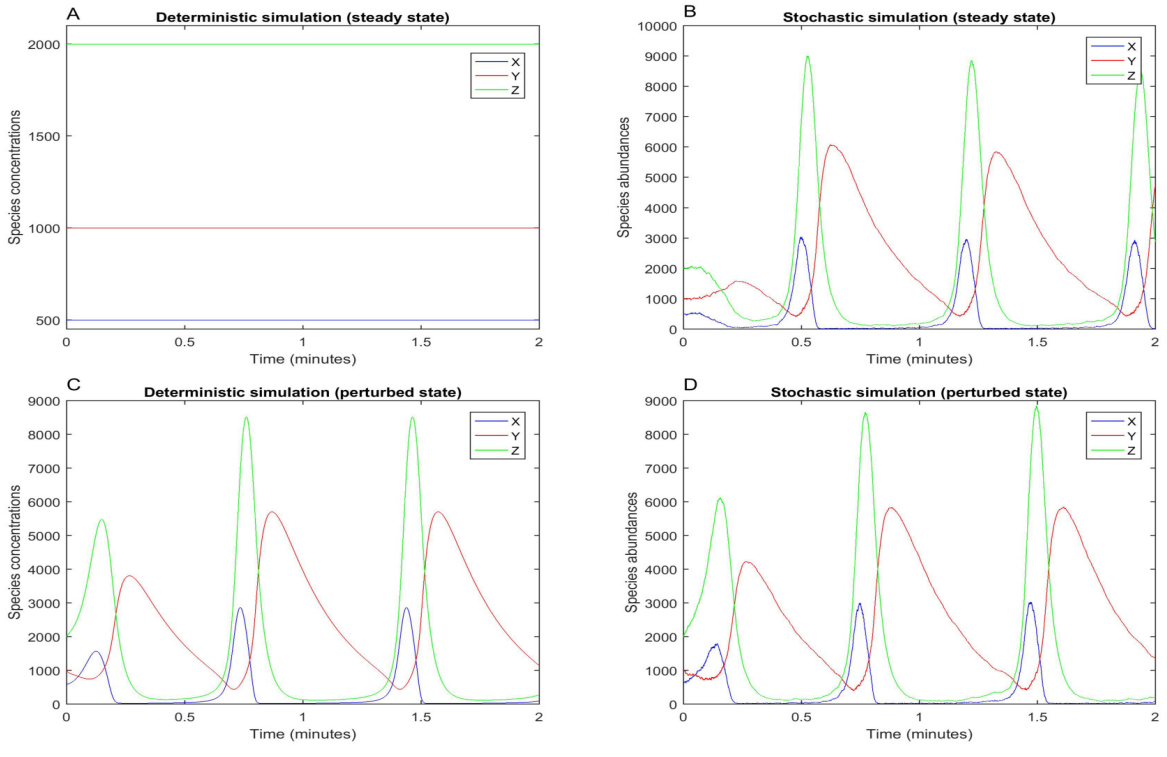

Fig. 1. The dynamics of the Oregonator model. (A) and (B) Model dynamics at the steady state ($c_1 = d_1 = 0.1, c_2 = d_2 = 2, c_3 = d_3 = 104, c_4 = 0.016, d_4 = 0.08, c_5 = d_5 = 26$ and $\#X_0 = [X_0] = 500, \#Y_0 = [Y_0] = 1000, \#Z_0 = [Z_0] = 2000$) in the deterministic and stochastic case. (C) and (D) Model dynamics from a perturbed state ($\#X = 600, \#Y = 1000, \#Z = 2000$, model parameters as in cases A and B) in the deterministic and stochastic case.

measures for the deterministic rates, which can be easily deduced as *ad hoc* ratios of concentration versus time [5].

3.1 The Oregonator model

The first model is a simplified version of a theoretical oscillator called *Oregonator* [26]. It has three species (X, Y and Z) and five reactions:

$$\begin{aligned} &R1 : X + Y \xrightarrow{c_1} \emptyset \qquad R2 : Y \xrightarrow{c_2} X \\ &R3 : X \xrightarrow{c_3} 2X + Z \quad R4 : 2X \xrightarrow{c_4} \emptyset \\ &R5 : Z \xrightarrow{c_5} Y, \end{aligned} \tag{23}$$

where the symbol $\emptyset$ is used for degradation.
This set or reactions corresponds to the following set of ODEs:

$$\begin{aligned} \tfrac{d[X]}{dt} &= -d_1[X][Y] + d_2[Y] + d_3[X] - 2d_4[X]^2 \\ \tfrac{d[Y]}{dt} &= -d_1[X][Y] - d_2[Y] + d_5[Z] \\ \tfrac{d[Z]}{dt} &= d_3[X] - d_5[Z]. \end{aligned} \tag{24}$$

For this model, a predefined set of rate parameters and initial values can lead the system dynamics to a steady state condition, which makes the computation of the three derivatives all equal to zero (see Fig.1A). This behaviour never occurs when stochastic simulation is employed, because when reactions are fired one after the other in an asynchronous way, the system immediately exits from the equilibrium and starts oscillating (see Fig.1B). To analyse the impact of this discrepancy between the two approaches, we will compare the sensitivity results for this model in two cases: (i) in a perturbed state, where the ODEs are not equal to zero (Fig.1C–D), and (ii) in the steady state condition (Fig.1A–B).

In Fig.2, the sensitivity results of the model around the perturbed state are presented. The figure shows that both the deterministic and the stochastic approaches provide similar results. As expected, we see a perfect overlap of the two deterministic methods (Fig.2A). The same happens for

Table 1. Methods' runtime for the Oregonator model around the perturbed state.

Stochastic approach					
Comp. time	GT	IRN	CRN	CFD	RFD
Mean ± SD	0.33±0.24 s	0.57±0.39 s	0.57±0.38 s	0.49±0.34 s	0.27± 0.23 s
Total (10,000 runs)	36.91 h	63.78 h	63.61 h	54.43 h	30.27 h
Deterministic approach					
Comp. time	FD method		Direct differential method		
	2.52 s		0.34 s		

Table 2. Methods' runtime for the Oregonator model around the steady state.

Stochastic approach					
Comp. time	GT	IRN	CRN	CFD	RFD
Mean ± SD	0.33±0.25 s	0.57±0.39 s	0.57±0.39 s	0.53±0.37 s	0.50±0.58 s
Total (10,000 runs)	36.27 h	63.18 h	63 h	58.50 h	55.98 h
Deterministic approach					
Comp. time	FD method		Direct differential method		
	1.05 s		0.08 s		

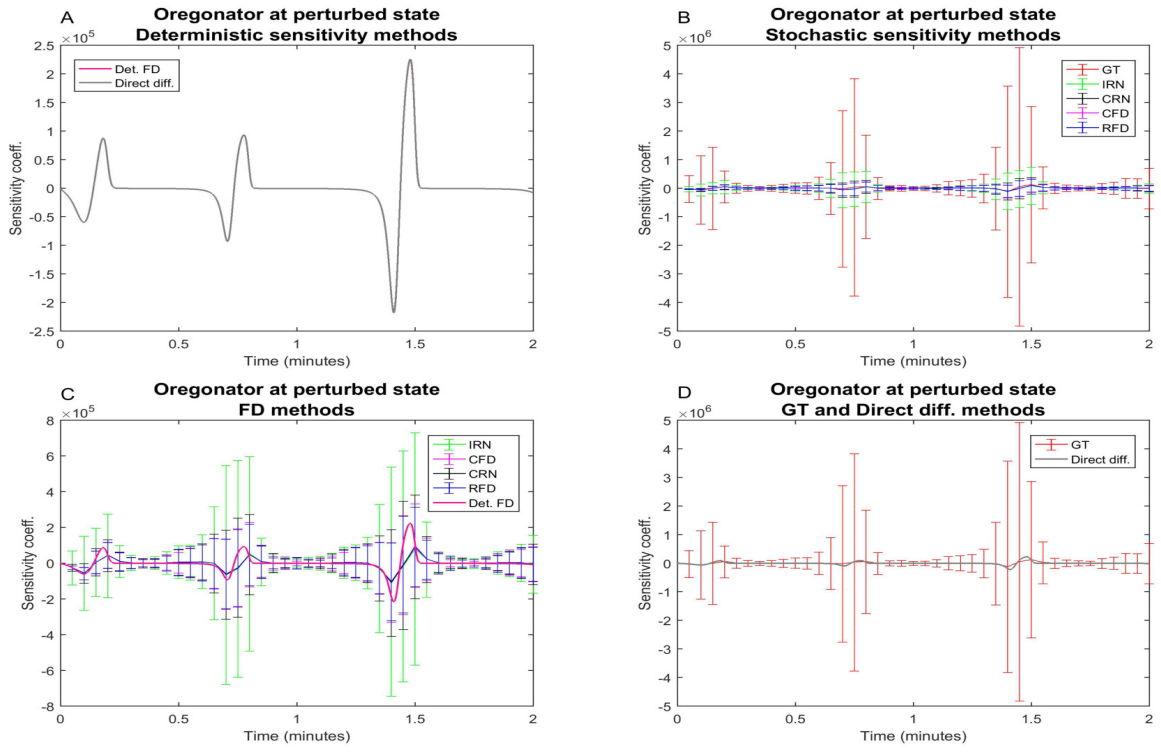

Fig. 2. Results for the sensitivity analysis computed on the Oregonator model around the perturbed state for parameters d_1 and c_1 on variable X. (A) Sensitivity results compared between the deterministic methods. (B) Sensitivity results compared between the stochastic methods. (C) Sensitivity results compared between the FD methods. (D) Sensitivity results compared between the "exact" methods.

the average of the five stochastic methods (Fig.2B), which mainly differ in terms of result variance. The average result of the stochastic methods also overlaps with the one of the deterministic simulation (Fig.2C and Fig.2D). However, the computational time required by the two approaches is very different (see Tab.1). Each stochastic method needs more than one day to compute the $10,000$ simulations required to derive the sensitivity coefficient, while only few seconds are needed in the deterministic case. Among all the stochastic methods, RFD is the one providing the lowest runtime and result variance. On the contrary, the GT algorithm is the one providing the largest result variance.

The quite close overlap between the deterministic and the stochastic framework does not hold when parameter sensitivity is computed at the model steady state (Fig.3). In such a case we observe that the sensitivity results are different between the two approaches. The two deterministic methods exhibit instability, which can be clearly appreciated for the direct differential method (Fig.3A). For what concerns the FD method, we observed that if we decrease the approximation error (by decreasing ϵ), the amplitude of the oscillations of the sensitivity coefficient increases correspondently, suggesting that also this method is not stable. This is due to the fact that a very small perturbation of model parameters is enough to exit from the steady state and this makes the deterministic approach unreliable independently from the employed integration method or the adopted tolerance value. This, however, never happens in the stochastic framework, where the random nature of the approach prevents the system to be in the steady state. For this reason, the computational time of deterministic methods listed in Tab.2 is not informative, while we can notice that the stochastic algorithms require a similar computational effort as given in Tab.1. Although RFD is not the fastest method, it is still the best compromise between computational time and variance.

3.2 The Oscillator model

The Oscillator [27] model is a noise-induced system with three species (A, B and C) and three reactions:

$$\begin{aligned} R1 &: A + B \xrightarrow{c_1} 2B \\ R2 &: B + C \xrightarrow{c_2} 2C \\ R3 &: C + A \xrightarrow{c_3} 2A. \end{aligned} \tag{25}$$

The corresponding set of ODEs is:

$$\begin{aligned} \frac{d[A]}{dt} &= -d_1[A][B] + d_3[A][C] \\ \frac{d[B]}{dt} &= d_1[A][B] - d_2[B][C] \\ \frac{d[C]}{dt} &= d_2[B][C] - d_3[A][C]. \end{aligned} \tag{26}$$

The model exhibits a symmetrical bell shape that, in the deterministic framework, is preserved with a perpetual periodical oscillating behaviour along all simulation time (see Fig.4A). Conversely, in the stochastic framework the amplitude of the oscillations changes over time and this opens the possibility for one or two out of three species to disappear (zero abundance). When this happens, the oscillatory pattern of the system stops and no other reactions are fired (see Fig.4B).

Fig.5 shows the sensitivity results obtained from the different methods. Comparing the two deterministic methods (Fig.5A), we see a perfect overlap of the two methods. This means that the error introduced by the finite difference approximation can be considered to be irrelevant. We can also notice how the sensitivity function increases its oscillation amplitude over time. This happens because perturbing a model parameter affects the frequency of the oscillations. As a result, the nominal and the perturbed state become increasingly out of sync over time. This explains both the periodicity of the sensitivity function and the increasing amplitude of its oscillations. We refer to [28; 29; 30] as a first look to the vast literature

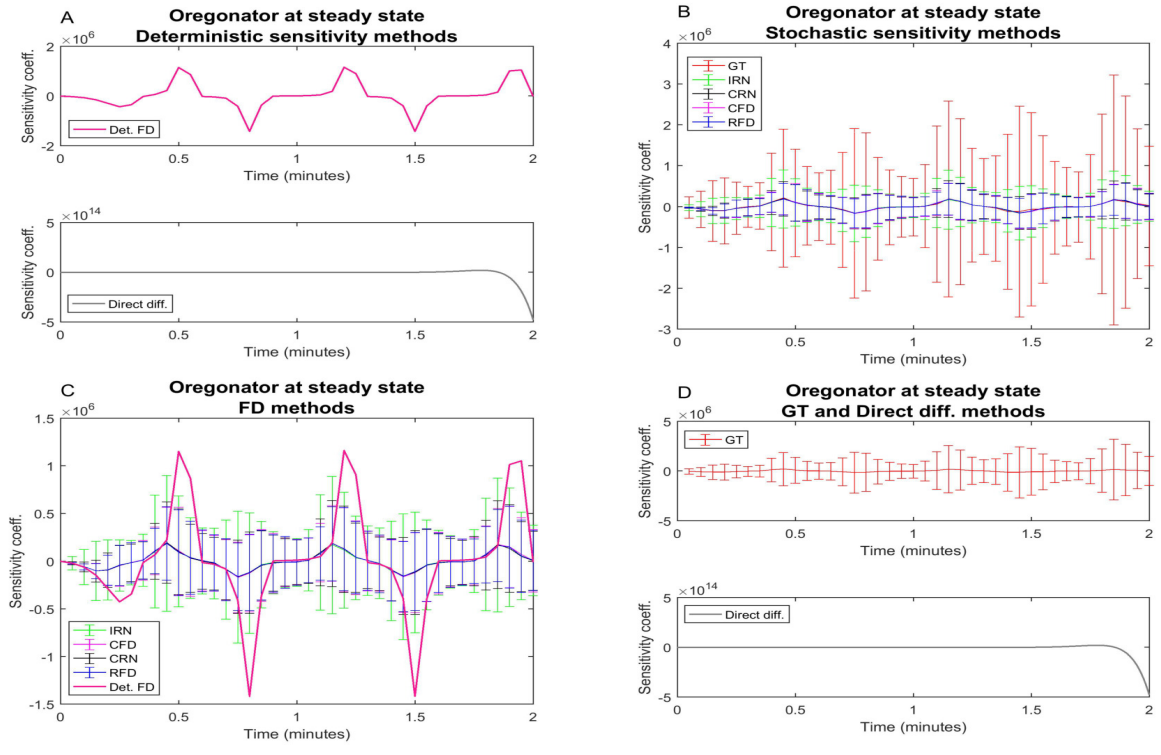

Fig. 3. Results for the sensitivity analysis computed on the Oregonator model around the steady state for parameters d_1 and c_1 on variable X. (A) Sensitivity results compared between the deterministic methods. (B) Sensitivity results compared between the stochastic methods. (C) Sensitivity results compared between the FD methods. (D) Sensitivity results compared between the "exact" methods.

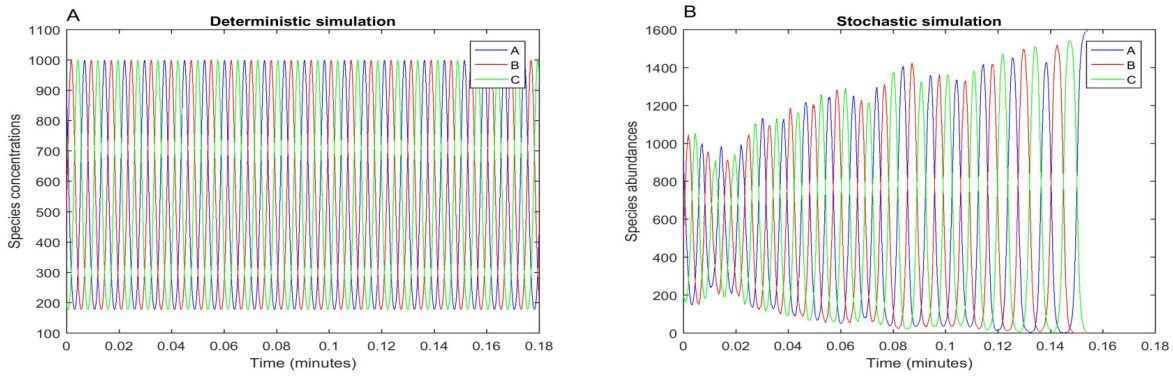

Fig. 4. Species dynamics for the Oscillator model. (A) Model dynamics computed with the deterministic approach ($d_1 = 1, d_2 = 1, d_3 = 1$ and $[A_0] = 900, [B_0] = 500, [C_0] = 200$). (B) One possible model dynamics computed with the stochastic approach ($c_1 = 1, c_2 = 1, c_3 = 1$ and $\#A_0 = 900, \#B_0 = 500, \#C_0 = 200$). In this case species B and C died at time 0.15m and this event stops the oscillatory pattern of the model.

dealing with sensitivity analysis of oscillatory systems, which is more focused on quantities of oscillations such as period and amplitude. Among the stochastic methods, we see that the GT method has the largest variance with respect to all the other methods (Fig.5B and Fig.5D). Moreover, all the stochastic methods have a large result variance. This is because in the $10,000$ simulations used to derive the sensitivity a wide range of possibilities are explored, with simulations that oscillate for all the simulation time, while other stop at some time because some model variables go to zero. Looking at Fig.5B and Fig.5D, we observe how deterministic and stochastic approaches provide different results. In fact, after a certain amount of time, the mean of the stochastic approach does not overlap anymore with the deterministic approach. This can be better appreciated in Fig.6 where Fig.5B and Fig.5D are zoomed to provide the firsts 2 and 6 oscillation periods. At the very beginning, the sensitivity values computed by the two approaches overlap (Fig.6A and Fig.6C), while they step by step decouple as the simulation time progresses (Fig.6B and Fig.6D).

As expected, the computational time required by the stochastic methods is still higher than the one of deterministic methods (see Tab.3).

3.3 The Schlögl model

The Schlögl model [31] is a reaction network that exhibits *bistability* and switching behaviour [32; 33; 34]. The system has two stable steady states separated by an unstable state. The model consists of three species (A, B

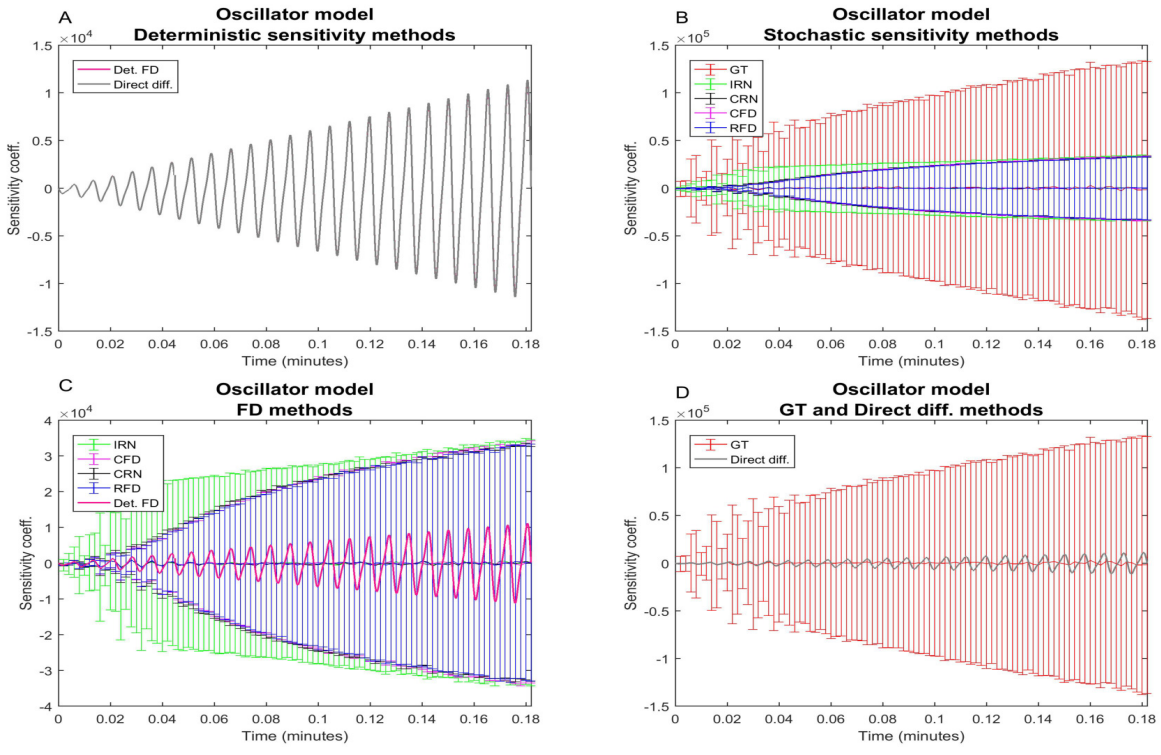

Fig. 5. Results for the sensitivity analysis computed on the Oscillator model for parameters d_1 and c_1 on variable A. (A) Sensitivity results compared between the deterministic methods. (B) Sensitivity results compared between the stochastic methods. (C) Sensitivity results compared between the FD methods. (D) Sensitivity results compared between the "exact" methods.

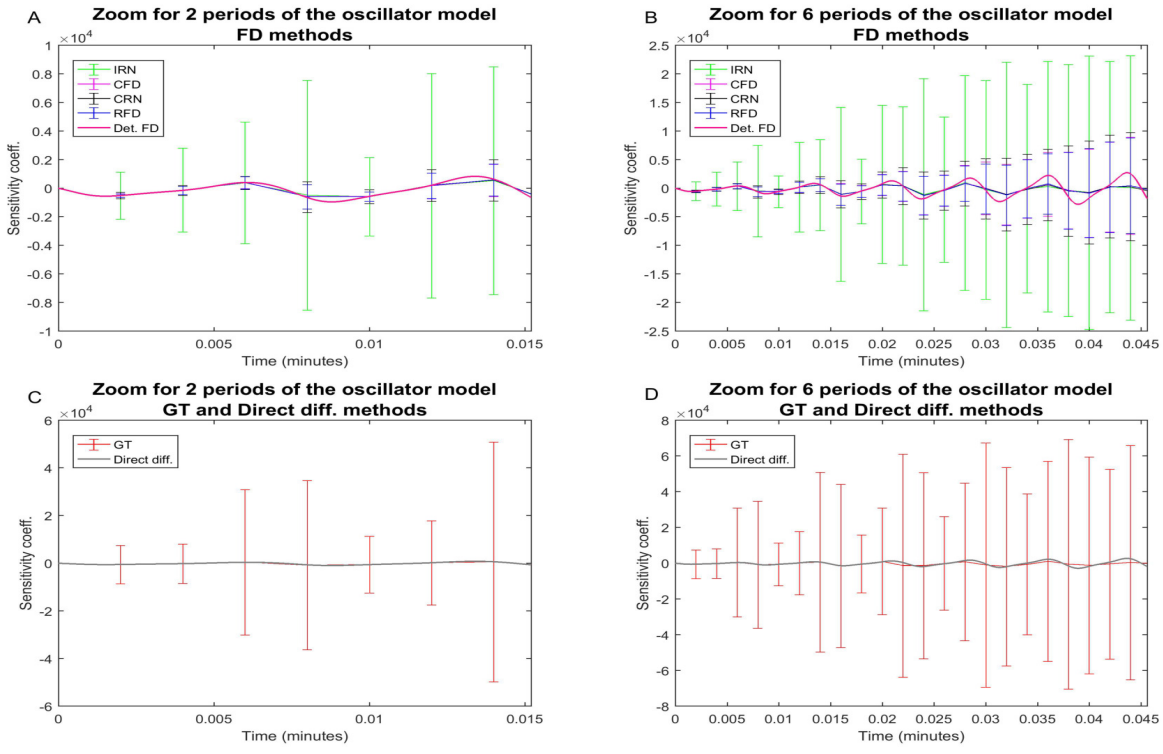

Fig. 6. Zoom for 2 and 6 periods for the sensitivity analysis computed on the Oscillator model for parameters d_1 and c_1 on variable A. (A) and (B) Results computed with the FD methods. (C) and (D) Results computed with the "exact" methods.

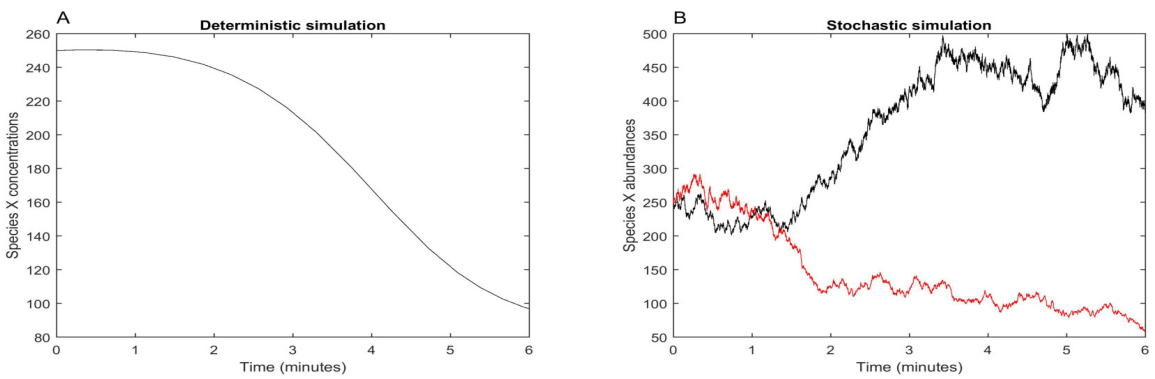

Fig. 7. Dynamics of species X of the Schlögl model. (A) Model dynamics computed with the deterministic approach ($d_1 = 1.5 \cdot 10^{-7}$, $d_2 = 1.67 \cdot 10^{-5}$, $d_3 = 1.0 \cdot 10^{-4}$, $d_4 = 3.5$ and $[A_0] = 100000$, $[B_0] = 200000$, $[X_0] = 250$). (B) Two possible model dynamics computed with the stochastic approach ($c_1 = 3.0 \cdot 10^{-7}$, $c_2 = 1.0 \cdot 10^{-4}$, $c_3 = 1.0 \cdot 10^{-3}$, $c_4 = 3.5$ and $\#A_0 = 100000$, $\#B_0 = 200000$, $\#X_0 = 250$). The difference between the two dynamics shows the bistability of the model in the stochastic framework.

Table 3. Methods' runtime for the Oscillator model.

Stochastic approach					
Comp. time	GT	IRN	CRN	CFD	RFD
Mean ± SD	0.14±0.13 s	0.26±0.22 s	0.26±0.21 s	0.22±0.19 s	0.21±0.21 s
Total (10,000 runs)	34.36 h	66.96 h	66.20 h	54.72 h	53.29 h
Deterministic approach					
Comp. time	FD method		Direct differential method		
	1.78 s		0.39 s		

and X) and four reactions:

$$\begin{aligned} R1 &: A + 2X \xrightarrow{c_1} 3X \quad R2 : 3X \xrightarrow{c_2} A + 2X \\ R3 &: B \xrightarrow{c_3} X \qquad\quad R4 : X \xrightarrow{c_4} B. \end{aligned} \tag{27}$$

The corresponding set of ODEs is:

$$\begin{aligned} \frac{d[A]}{dt} &= -d_1[A][X]^2 + d_2[X]^3 \\ \frac{d[B]}{dt} &= -d_3[B] + d_4[X] \\ \frac{d[X]}{dt} &= d_1[A][X]^2 - d_2[X]^3 + d_3[B] - d_4[X]. \end{aligned} \tag{28}$$

In the deterministic framework, the system converges to one of the two steady states depending on the initial state (see Fig.7A). Instead, in the stochastic framework, the system may jump between the two stable states spontaneously, due to its inherent randomness, creating a behaviour that cannot be observed in the deterministic framework (see Fig.7B and Fig.8). For this model we only provide the results for the species X because species A and B are large and are assumed to remain essentially constant over the simulation time.

In Fig.9, we report the results of the sensitivity analysis. Looking at Fig.9A, we notice that the sensitivity values obtained by the two deterministic methods do not overlap. This approximation can be overcome with a smaller choice of ϵ (see Fig.9A, dashed line). This means that for this model the approximation introduced by the FD method is not negligible with the choice of $\epsilon = 0.01$. Also, the results show that the mean of the sensitivity values computed with the stochastic methods never overlaps the deterministic one (Fig.9C). In fact, only with the stochastic approach the bistability nature of the model can be appreciated. The occurrence of bistability also explains why the variance of all the stochastic algorithms increases until a certain time point (close to 10). From time 10

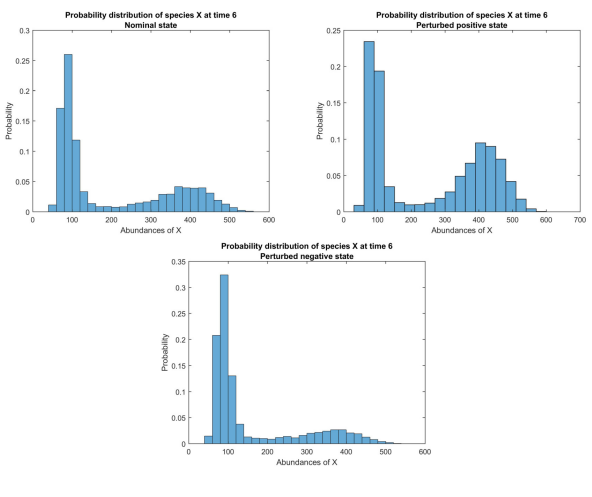

Fig. 8. Histogram of species X at time 6 calculated by 10,000 stochastic simulation runs. The x-axis is the interval of population of species X. The y-axis is the probability for species X to be in the corresponding interval. The figure shows the bistability of the model since at time 6 the population of species X fluctuates around two peaks (close to 100 and 400) for all the three considered cases: nominal state (X^{c_1}), perturbed positive state ($X^{c_1+\epsilon c_1}$) and perturbed negative state ($X^{c_1-\epsilon c_1}$).

to time 15, the second stable state becomes a rare event and, as can be seen in Fig.10, all the system states end up around the value of 90. However, the variance still remains high due to the small value of the parameter c_1, which produces an high sensitivity value.

The computational time required by the two approaches is lower than for all the other considered models. The means of the stochastic methods are comparable with the deterministic direct differential method (see Tab.4) and RFD is still the best option in terms of low computational time and small variance.

4 Conclusions

This paper compares the stochastic and the deterministic sensitivity analysis for biochemical reaction systems. Three theoretical models have been considered to test the computational approaches in specific conditions where stochastic and deterministic simulation yield different results (the Oregonator model for systems with unstable steady states, the Oscillator model for oscillators with population extinction and the Schlögl model for

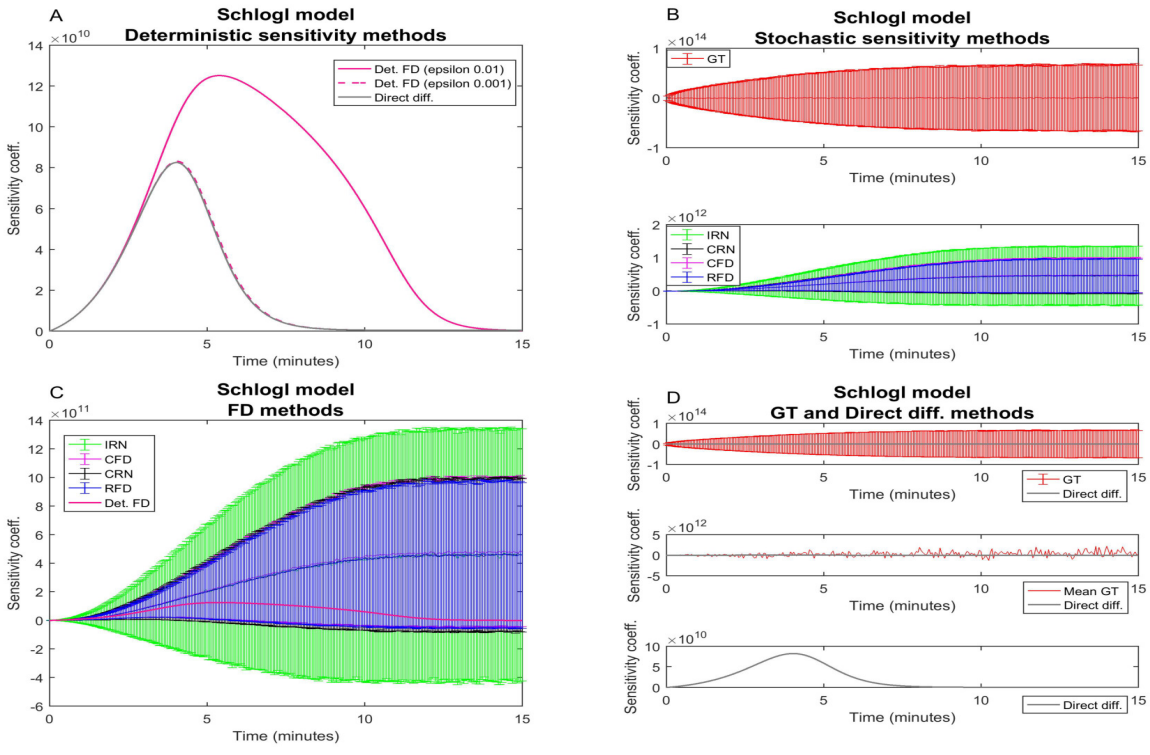

Fig. 9. Results for the sensitivity analysis computed on the Schlögl model for parameters d_1 and c_1 on variable X. (A) Sensitivity results compared between the deterministic methods. The dashed line provides the output of the FD method with $\epsilon = 0.001$. (B) Sensitivity results compared between the stochastic methods. (C) Sensitivity results compared between the FD methods. (D) Sensitivity results compared between the "exact" methods.

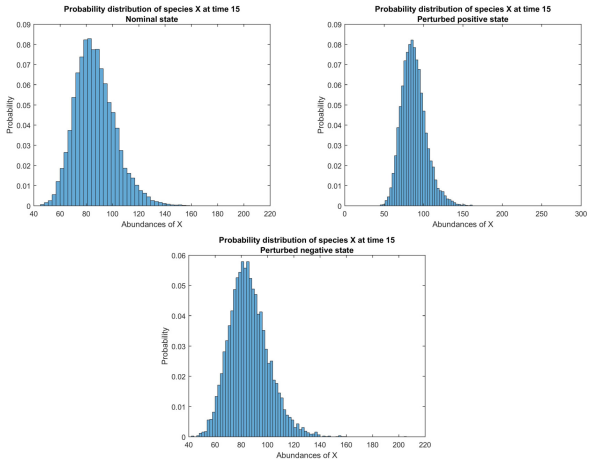

Fig. 10. Histogram of species X at time 15 calculated by 10,000 simulation runs. The x-axis is the interval of population of species X. The y-axis is the probability for species X to be in the corresponding interval. The figure shows that at time 15 the second state (the one close to 400) becomes a rare event for all the three considered cases: nominal state (X^{c_1}), perturbed positive state ($X^{c_1+\epsilon c_1}$) and perturbed negative state ($X^{c_1-\epsilon c_1}$).

bistable systems). Our comparison shows that both approaches have some pros and cons as summarized in Fig. (11).

The results for the Oregonator model underline how the deterministic approach is not able to deal with the steady state condition that, for this model, is so different with respect to the one of the perturbed state. This instability could be an important limitation of the method because the steady state condition is often used in the deterministic approach for

Table 4. Methods' runtime for the Schlögl model.

Stochastic approach					
Comp. time	GT	IRN	CRN	CFD	RFD
Mean ± SD	0.03±0.04 s	0.06±0.05 s	0.05±0.06 s	0.04±0.05 s	0.03±0.04s
Total (10,000 runs)	24.93 h	44.59 h	44.69 h	39.88 h	27.95 h
Deterministic approach					
Comp. time	FD method		Direct differential method		
	0.15 s		0.04 s		

parameter calibrations. Moreover, the deterministic approach is unable to show the specific model behaviour that is expressed only when the randomness nature of the system is considered. In fact, the deterministic and stochastic approaches show the same results for the Oregonator model around the perturbed state as the system has the same behaviour. Instead, for the Oscillator and the Schlögl model, the results are different because the two systems have different behaviour in the two conditions. This point is very important because, given the high computational cost of sensitivity analysis, a relatively small number of modeling works rely on the stochastic approach to compute the sensitivity analysis. Moreover, in some of these works the impact of such a choice might have been underestimated. To this regard, on the top of the three conditions considered in the review, only the risk of population extinction could be potentially predicted when deterministic simulation is employed. Indeed, this is a direct consequence of low numbered species that can be observed also by deterministic simulation. Conversely, the other two conditions can be identified only

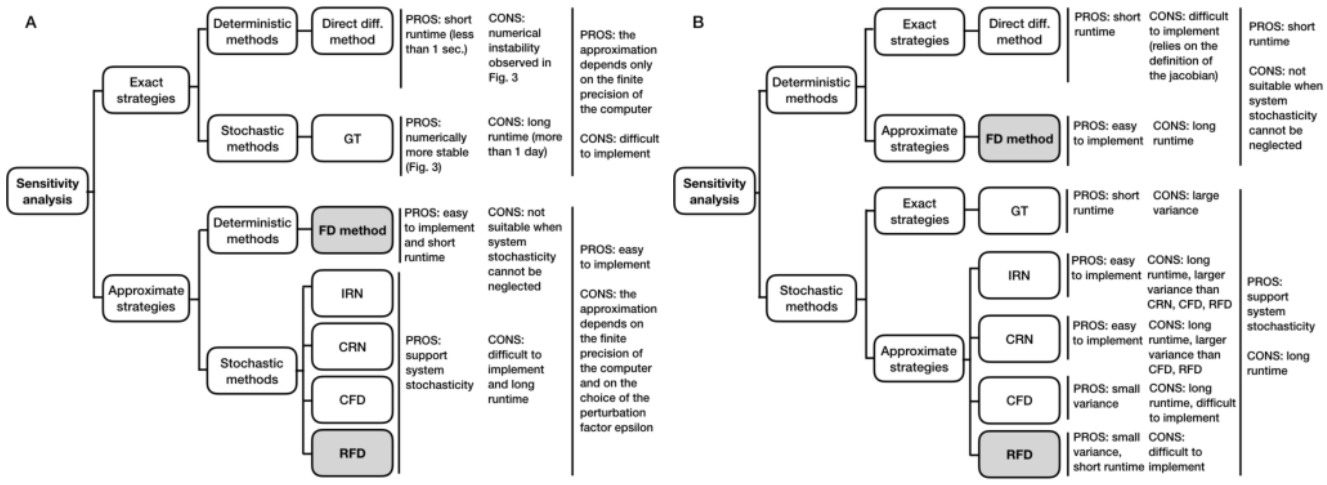

Fig. 11. Graphical comparison of the reviewed methods for computing sensitivity analysis. For each computational approach the most important pros and cons are indicated. The FD and the RFD methods are highlighted in grey to indicate that these are the methods providing the best performances, on average, in all the case studies presented in the review. (A) The methods are firstly divided in exact and approximate strategies. (B) The methods are firstly divided in deterministic and stochastic methods.

if the modeler tries to also simulate the system by stochastic simulation. In our experience, it would be good to run some stochastic simulations of the model to check that the stochastic behaviour of the system does not deviate too much from the deterministic one. When this happens, deterministic simulation should not be used. This preliminary checking, however, could be computationally demanding in case of large models or in case of a large set of repeated analyses.

The limitations of the stochastic framework are the large variance of their estimates and the computational time. In all of our test cases, the GT method has the largest variance and most of the time the shortest runtime. For the four FD methods considered, IRN has the largest variance and the shortest simulation time. In terms of simulation time, IRN showed a computational time that is comparable with CRN even if this method showed a smallest variance with respect to IRN. Additionally, even if the CFD and RFD showed similar results in terms of variance, RFD often has the lowest computational time.

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Key points

- Sensitivity analysis is emerging as an important tool for investigating mathematical models of biological dynamics.
- The deterministic and the stochastic approaches for computing sensitivity analysis can provide very different results in conditions where deterministic simulation is unable to capture the exact evolution in time of the biological system (systems with unstable steady states, oscillators with population extinction, bistable systems).
- Despite the fact that steady state analysis is very popular in deterministic modeling, the deterministic approach exhibited numerical instability in specific conditions when the sensitivity has been computed at the model steady state.
- Stochastic methods take into account system stochasticity, but they are often affected by the large variance of the results and a long computational time.
- RFD resulted to be the best compromise among the stochastic algorithms in terms of variance and computational cost.

Biographical notes

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Luca Marchetti, PhD, is the Head of the Computational Biology team at COSBI. He is also Contract Professor at the University of Verona, and an Associate Editor of the journal Optimization, Frontiers in Applied Mathematics and Statistics. He is in charge of several research projects in collaboration with important universities and pharmaceutical companies, and he is the author of scientific papers in international journals, books and conference proceedings.

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Figure legends

Fig. 1 The dynamics of the Oregonator model. (A) and (B) Model dynamics at the steady state ($c_1 = d_1 = 0.1, c_2 = d_2 = 2, c_3 = d_3 = 104, c_4 = 0.016, d_4 = 0.08, c_5 = d_5 = 26$ and $\#X_0 = [X_0] = 500, \#Y_0 = [Y_0] = 1000, \#Z_0 = [Z_0] = 2000$) in the deterministic and stochastic case. (C) and (D) Model dynamics from a perturbed state ($\#X = 600, \#Y = 1000, \#Z = 2000$, model parameters as in cases A and B) in the deterministic and stochastic case.

Fig. 2 Results for the sensitivity analysis computed on the Oregonator model around the perturbed state for parameters d_1 and c_1 on variable X. (A) Sensitivity results compared between the deterministic methods. (B) Sensitivity results compared between the stochastic methods. (C) Sensitivity results compared between the FD methods. (D) Sensitivity results compared between the "exact" methods.

Fig. 3 Results for the sensitivity analysis computed on the Oregonator model around the steady state for parameters d_1 and c_1 on variable X. (A) Sensitivity results compared between the deterministic methods. (B) Sensitivity results compared between the stochastic methods. (C) Sensitivity results compared between the FD methods. (D) Sensitivity results compared between the "exact" methods.

Fig. 4 Species dynamics for the Oscillator model. (A) Model dynamics computed with the deterministic approach ($d_1 = 1, d_2 = 1, d_3 = 1$ and $[A_0] = 900, [B_0] = 500, [C_0] = 200$). (B) One possible model dynamics computed with the stochastic approach ($c_1 = 1, c_2 = 1, c_3 = 1$ and $\#A_0 = 900, \#B_0 = 500, \#C_0 = 200$). In this case species B and C died at time 0.15m and this event stops the oscillatory pattern of the model.

Fig. 5 Results for the sensitivity analysis computed on the Oscillator model for parameters d_1 and c_1 on variable A. (A) Sensitivity results compared between the deterministic methods. (B) Sensitivity results compared between the stochastic methods. (C) Sensitivity results compared between the FD methods. (D) Sensitivity results compared between the "exact" methods.

Fig. 6 Zoom for 2 and 6 periods for the sensitivity analysis computed on the Oscillator model for parameters d_1 and c_1 on variable A. (A) and (B) Results computed with the FD methods. (C) and (D) Results computed with the "exact" methods.

Fig. 7 Dynamics of species X of the Schlögl model. (A) Model dynamics computed with the deterministic approach ($d_1 = 1.5 \cdot 10^{-7}, d_2 = 1.67 \cdot 10^{-5}, d_3 = 1.0 \cdot 10^{-4}, d_4 = 3.5$ and $[A_0] = 100000, [B_0] = 200000, [X_0] = 250$). (B) Two possible model dynamics computed with the stochastic approach ($c_1 = 3.0 \cdot 10^{-7}, c_2 = 1.0 \cdot 10^{-4}, c_3 = 1.0 \cdot 10^{-3}, c_4 = 3.5$ and $\#A_0 = 100000, \#B_0 = 200000, \#X_0 = 250$). The difference between the two dynamics shows the bistability of the model in the stochastic framework.

Fig. 8 Histogram of species X at time 6 calculated by 10,000 stochastic simulation runs. The x-axis is the interval of population of species X. The y-axis is the probability for species X to be in the corresponding interval. The figure shows the bistability of the model since at time 6 the population of species X fluctuates around two peaks (close to 100 and 400) for all the three considered cases: nominal state (X^{c_1}), perturbed positive state ($X^{c_1+\epsilon c_1}$) and perturbed negative state ($X^{c_1-\epsilon c_1}$).

Fig. 9 Results for the sensitivity analysis computed on the Schlögl model for parameters d_1 and c_1 on variable X. (A) Sensitivity results compared between the deterministic methods. The dashed line provides the output of the FD method with $\epsilon = 0.001$. (B) Sensitivity results compared between the stochastic methods. (C) Sensitivity results compared between the FD methods. (D) Sensitivity results compared between the "exact" methods.

Fig. 10 Histogram of species X at time 15 calculated by 10,000 simulation runs. The x-axis is the interval of population of species X. The y-axis is the probability for species X to be in the corresponding interval. The figure shows that at time 15 the second state (the one close to 400) becomes a rare event for all the three considered cases: nominal state (X^{c_1}), perturbed positive state ($X^{c_1+\epsilon c_1}$) and perturbed negative state ($X^{c_1-\epsilon c_1}$).

Fig. 11 Graphical comparison of the reviewed methods for computing sensitivity analysis. For each computational approach the most important pros and cons are indicated. The FD and the RFD methods are highlighted in grey to indicate that these are the methods providing the best performances, on average, in all the case studies presented in the review. (A) The methods are firstly divided in exact and approximate strategies. (B) The methods are firstly divided in deterministic and stochastic methods.