Sensitivity Analysis of Discrete Stochastic Biological Systems

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Abstract

Sensitivity analysis quantifies the dependence of system "behavior" on the parameters that affect the process dynamics. Classical sensitivity analysis, however, does not directly apply to discrete stochastic dynamical systems, which have recently gained popularity because of its relevance to biological processes. In this work, the sensitivity analysis for discrete stochastic processes is developed based on density function (distribution) sensitivity, using an analog of the classical sensitivity and the Fisher Information Matrix. There exist many circumstances, such as in systems with multistability, in which the stochastic effects become nontrivial and classical sensitivity analysis on deterministic representation of the system cannot adequately capture the true system behavior. The proposed analysis is applied to a bistable chemical system - the Schlögl model [1], and to a synthetic genetic toggle switch model [2]. Comparisons between the stochastic and deterministic analysis show the significance of explicit consideration of the probabilistic nature in the sensitivity analysis for this class of processes.

1 Introduction

Traditionally, the concept of sensitivity applies to continuous deterministic systems, *e.g.*, systems described by differential (or differential-algebraic) equations. The sensitivity coefficients are given by [3]

$$S_{i,j} = \frac{\partial y_i(t)}{\partial p_j} \tag{1}$$

where y_i denote the i-th output, t time, and p_j the j-th parameter. Although this concept has wide applicability, it does not directly apply to stochastic/probabilistic systems whose outputs take random values with probability defined by a density function. Nevertheless, sensitivity analysis of stochastic differential equations has been previously developed [4, 5] where the stochastic effects enter as additive Gaussian white noise in the differential equation (*e.g.* Langevin-type problems).

Discrete stochastic modeling has recently gained popularity because of its relevance in biological processes [6, 7] which achieve their functions with low copy numbers of some key chemical species. Unlike the solutions to stochastic differential equations, the states/outputs of discrete stochastic systems evolve according to discrete jump Markov processes, which naturally leads to a probabilistic description of the system dynamics. The states and outputs are random variables governed by a probability density function which follows a chemical master equation (CME) [1]. The rate of reaction no longer describes the amount of chemical species being produced or consumed

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per unit time in a reaction, but rather the likelihood of a certain reaction to occur. Though analytical solution of the CME is rarely available, the density function can be constructed using the Stochastic Simulation Algorithm [8].

This work aims to develop an analog of parametric sensitivity for discrete stochastic systems. Four sensitivity measures were formulated based on a direct extension of the deterministic sensitivity and on the Fisher Information Matrix (FIM) from information theory [9]. In addition, the stochastic effects in certain systems can give rise to distinctive density functions, involving multimodality, which necessitate application of the proposed analysis. The proposed analysis was applied to two representative examples depicting these circumstances: a prototype chemical reaction network - the Schlögl model [1], and a model for a synthetic genetic toggle switch in *E. coli* [2]. The toggle switch consists of two repressor-promoter pairs aligned in a mutually inhibitory network. Comparisons of classical and stochastic sensitivity analysis demonstrate the significance of an explicit treatment of the probabilistic behavior in the analysis of these systems.

2 Discrete Stochastic Sensitivity Analysis

In discrete stochastic systems, the states and outputs are random variables characterized by a probability density function (pdf). The sensitivity as defined in Eq. 1 requires continuity of the outputs with respect to the parameters and hence does not directly apply to discrete stochastic outputs. However, the notion of sensitivity suitably applies to the density function which characterizes the system outputs. Hence, a direct analog of classical parametric sensitivity in Eq. 1 for a discrete stochastic system is given by [4]:

$$S_j(\mathbf{x},t) = \frac{\partial f\left(\mathbf{x}(\mathbf{p}),t\right)}{\partial p_j} \tag{2}$$

where f is the density function, $\mathbf{x}$ denote the vector of states and outputs, and $\mathbf{p}$ denote the vector of parameters. The aforementioned sensitivity yields a sensitivity measure for discrete stochastic systems:

$$S_j(t) = E\left[\left|\frac{\partial f\left(\mathbf{x},t\right)}{\partial p_j}\right|\right] = \int_{\mathbf{X}} \left|\frac{\partial f\left(\mathbf{x},t\right)}{\partial p_j}\right| f\left(\mathbf{x},t\right) d\mathbf{x} \tag{3}$$

An alternate measure of sensitivity comes from the field of information theory using the Fisher Information Matrix J [9]:

$$J = E\left[\nabla_{\mathbf{p}} \log f \nabla_{\mathbf{p}} \log f^T\right] \tag{4}$$

which defines the lower bound for the uncertainty in the parameter estimates according to the Cramer-Rao inequality

$$V_{\mathbf{p}} \geq J^{-1} \tag{5}$$

where $V_{\mathbf{p}}$ denotes the covariance of unbiased parameter estimates. If the density function follows a normal distribution, then the FIM simplifies to

$$J = S^T V^{-1} S \tag{6}$$

where S denotes the sensitivity matrix as defined in Eq. 1 and V^{-1} denotes the measurement covariance. Thus, under the Gaussian assumption, the FIM can be interpreted as a consolidation of (weighted) sensitivities. This simplified FIM provides the basis of past hybrid stochastic sensitivity analysis schemes [10]. Three sensitivity measures can be derived based on the FIM - the diagonal elements, the eigenvalues, and the inverse of standard deviations (*i.e.*, the inverse of the diagonals of $V_{\mathbf{p}}$).

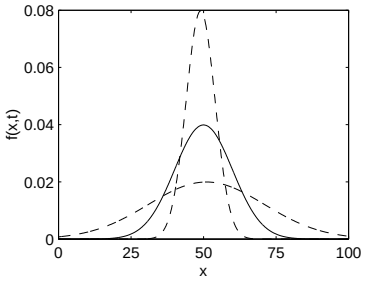

Fig. 1: Example of a sensitive distribution with insensitive mean value. The nominal distribution is shown in solid and the perturbed distributions are shown in dashed.

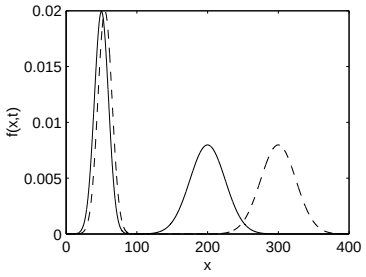

Fig. 2: A bistable system with different sensitivities between the two modes. The nominal distribution is shown in solid and the perturbed distribution in dashed.

3 Stochastic vs. Deterministic Analysis

Before proceeding to the application of the proposed sensitivity analysis, it is prudent to identify the stochastic circumstances under which the sensitivity analysis of deterministic models can potentially fail and thus necessitate the use of discrete stochastic analysis. The fundamental difference between the deterministic and stochastic analysis is in the type of system behavior changes that are measured in each analysis. The simplest example of such circumstances is shown in Figure 1. Here, the parameter perturbation induces large changes in the system entropy (uncertainty) [9] with inappreciable shift of the mean (mode). Assuming that the deterministic model represents the mean (mode) of the distribution, classical sensitivity analysis will incorrectly suggest that the system is insensitive to the parameter perturbation as the mean (mode) of the distribution changes very little. The stochastic analysis of this example will suggest a strong sensitivity with respect to this parameter by taking into account changes in the overall density function.

Another example can arise from a form of nonlinear dynamics, namely multistability. A deterministic multistable system occurs when there exists more than one attractor, for which small variations in the bifurcating variable will lead to very different steady states. Such mechanisms are believed to play an important role in biological systems, acting for example as dynamical switches [7]. In this case, the differences between the deterministic and stochastic analysis can arise in a situation such as shown in Figure 2. Due to the difference in the sensitivities of the attractors, the deterministic analysis will incorrectly suggest insensitivity to the parameter when the deterministic simulation converges to the left attractor; ignoring the sensitivity of the right modality.

Tab. 1: Schlögl Parameter Values

Parameter Index	Parameters	Values
1	Ak_1	3×10^{-2}
2	k_2	10^{-4}
3	Bk_3	2×10^2
4	k_4	3.5

4 Examples

The stochastic model of interest is described by a chemical master equation and simulated using the stochastic simulation algorithm (SSA) [8].

4.1 Schlögl Model

The Schlögl model describes a prototype chemical reaction network [1]

$$A + 2X \underset{a_2}{\overset{a_1}{\rightleftarrows}} 3X; \qquad B \underset{a_4}{\overset{a_3}{\rightleftarrows}} X \tag{7}$$

where the concentrations A and B are kept constant (buffered) and the reaction rate constants k_js are the model parameters. The propensity functions for these reactions follow

$$\begin{array}{ll} a_1 = k_1 AX(X-1)/2; & a_2 = k_2 X(X-1)(X-2)/6; \\ a_3 = k_3 B; & a_4 = k_4 X \end{array} \tag{8}$$

This system possesses two stable steady states for the parameter values in Table 1. Figure 3 shows the deterministic and SSA simulations of the Schlögl model for the two initial states $X(0) = 247$ and $X(0) = 250$. The deterministic simulation with smaller initial value converged to the left mode, and vice versa, the one with larger initial value to the right mode of the distribution. The bifurcation at approximate initial condition $X(0) \approx 248$ was apparent from the deterministic simulations, but the density functions from the stochastic simulations differed very little.

Here, we applied the stochastic sensitivity analysis to the Schlögl model around the bifurcation point $X(0) \approx 248$. As the deterministic and stochastic sensitivity coefficients have different units, the comparisons between the two analysis focus on the relative ordering of the parametric sensitivity magnitudes. Figure 4 shows the deterministic sensitivity orderings, while the corresponding stochastic sensitivities are shown in Figure 5. The first stochastic sensitivity measure ("direct" in Figure 5 corresponds to Eq. 3, while the remaining three represent the FIM-based sensitivity measures. The stochastic sensitivity measures were obtained from 100 independent samples of each sensitivity measure.

4.2 Genetic Toggle Switch

The second example is a model of a synthetic genetic toggle switch consisting of two repressor-promoter pairs, lacI repressor with Ptrc-2 promoter and a λ repressor cIts with P_Ls1con promoter,

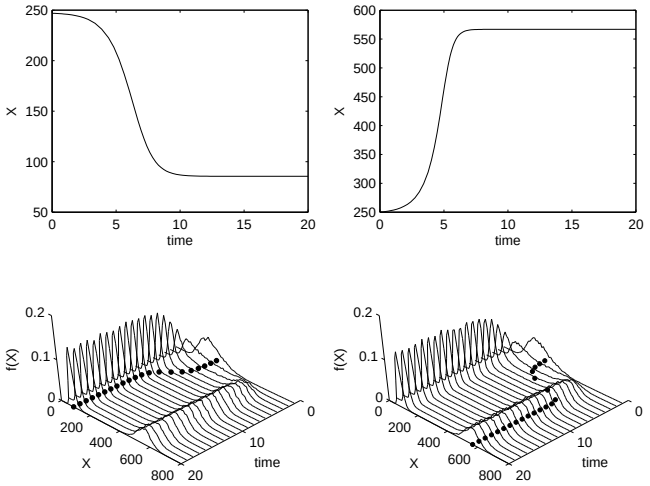

Fig. 3: Deterministic (top and bottom •) and SSA (bottom) simulations of bistable Schlögl model for the initial conditions $X(0) = 247$ (left) and $X(0) = 250$ (right). For ease of comparison, the state X from the deterministic and stochastic simulations were shown in comparable magnitudes despite having different units. Each distribution is constructed from 10000 realizations of the state X.

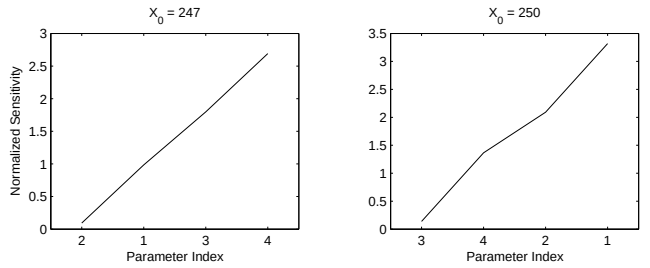

Fig. 4: Deterministic sensitivity ordering of the Schlögl model with initial condition near bifurcation.

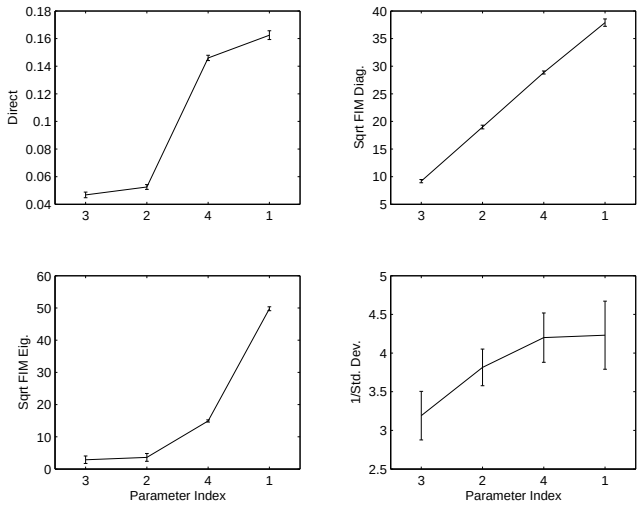

Fig. 5: Stochastic sensitivity ordering for the Schlögl model using different sensitivity measures near bifurcation.

Tab. 2: Genetic Toggle Switch Parameter Values

Index	Parameters	Values
1	α_1	156.25
2	α_2	15.6
3	β	2.5
4	γ	1
5	η	2.0015
6	K	6.0×10^{-5}

aligned in a mutually inhibitory manner [2]. Here, the expression of lacI represses the activity of Ptrc-2, which is the promoter of cIts, and vice versa, the expression of cIts inhibits the promoter P_Ls1con of lacI (see Figure 6). High expression of cIts will "light" up the cell, referred to as ON state, and vice versa high expresion of lacI as OFF state. Addition of the inducer isopropyl-β-D-thiogalactopyranoside (IPTG) will bias the distribution to the ON state [11]. A simple model for this system has been proposed, with two states describing the concentration of each repressor [2]:

$$\frac{d[\mathrm{lacI}]}{dt} = \frac{\alpha_1}{1 + [\mathrm{cIts}]^{\beta}} - [\mathrm{lacI}] \tag{9a}$$

$$\frac{d[\mathrm{cIts}]}{dt} = \frac{\alpha_2}{1 + [\mathrm{lacI}^*]^{\gamma}} - [\mathrm{cIts}] \tag{9b}$$

where

$$[\mathrm{lacI}^*] = \frac{[\mathrm{lacI}]}{(1 + [\mathrm{IPTG}]/K)^{\eta}} \tag{10}$$

The parameter values are listed in Table 2. The cells were initially grown in the OFF state.

For the aforementioned parameters, the system exhibits bistability [2]. Near the bifurcation point, the stochastic system exhibited a bimodal distribution associated with the ON and OFF states,

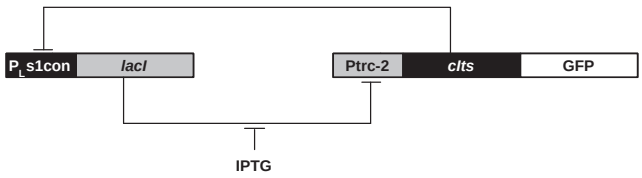

Fig. 6: Synthetic genetic toggle switch.

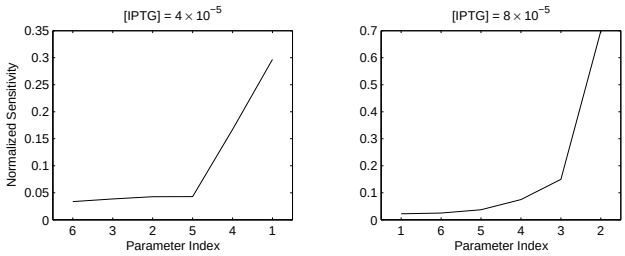

Fig. 7: Deterministic sensitivity ordering for the genetic toggle switch at different inducer concentrations. The bifurcation point occurs at $[\mathrm{IPTG}] = 7.95 \times 10^{-5}$.

and the stochastic effects introduced flip-flops between the two stable steady states. The bimodality exhibited at $[\mathrm{IPTG}]$ level as low as 3×10^{-5} (not shown), far less than the (deterministic) bifurcation point at $[\mathrm{IPTG}] = 7.95 \times 10^{-5}$. Figures 7 and 8 present the deterministic and stochastic sensitivity ordering near the bifurcation point ($[IPTG] = 4 \times 10^{-5}$).

5 Discussion

Comparisons among the sensitivity orderings in the two examples showed discrepancies between the deterministic and discrete stochastic analysis around the bifurcation point, in particular when the distribution function becomes bimodal. The main reason is that the stochastic analysis was able to capture the sensitivities of the two attractors simultaneously. In other words, the sensitivity features of both steady states concurrently affected the stochastic analysis, but not the deterministic analysis. In the Schlögl model, the two most sensitive parameters around the bifurcation point in the stochastic analysis were exactly the most sensitive parameters of both attractors independently, according to the deterministic analysis. Similarly, the stochastic sensitivity of the genetic toggle switch showed combinations of deterministic sensitivity ordering of the two attractors. Away from the bifurcation point however, the stochastic simulations gave unimodal distributions, and the stochastic and deterministic sensitive orderings exhibited good agreement (results not shown for brevity).

The four sensitivity measures were in good agreement with each other, despite the differences in their interpretations. The direct and FIM diagonals are closely related to the first order sensitivity such as Eq. 1, from their definitions. The FIM eigenvalues and the standard deviations have less direct correlation with the classical sensitivity, but they carry additional information about the system behavior under simultaneous multiple parameter perturbations. These measures are closely related to information content and parametric uncertainty in parameter estimation problems. The standard deviations provided a sensitivity measure with higher variations than the others due

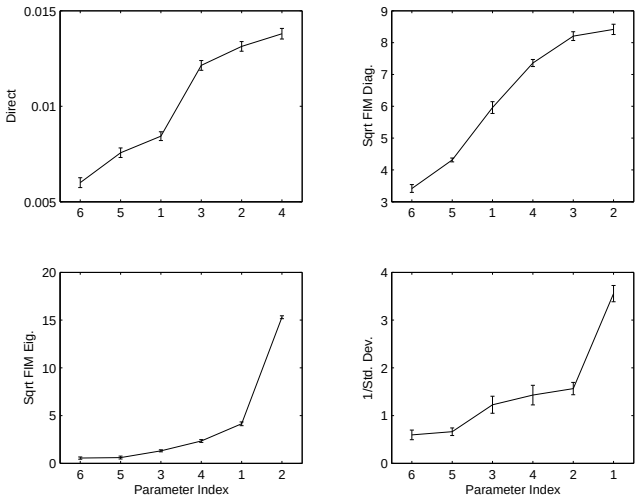

Fig. 8: Stochastic sensitivity ordering for the genetic toggle switch at an inducer concentration $[\mathrm{IPTG}] = 4.0 \times 10^{-5}$.

to numerical sensitivity of the matrix inversion required in their calculation.

The differences between the classical and stochastic analysis above give support for rigorous consideration of the stochastic effects in studying small systems. The genetic toggle switch example also motivates explicit treatment of the stochastic effects in model development and parameter estimation, in particular, the early onset of bifurcation. Similar behavior around the bifurcation point has also been observed in the Hopf bifurcation of of *Drosophila* Circadian rhythm, leading to an early onset of oscillations [12]. In such situations, stochastic paradigms such as the CME or chemical Langevin equation can provide information on the system dynamics that is missing from deterministic models.

6 Conclusions

Sensitivity analysis of discrete stochastic processes incorporates the dynamics of the density function explicitly. In small systems exhibiting multistability, the stochastic effects around the bifurcation point manifest as multimodal density functions and spread out the transitions between different steady states (*i.e.*, the stochastic effects annihilate the bifurcation between steady states). The deterministic and stochastic sensitivity analysis around such a bifurcation point can lead to different conclusions, as the deterministic model lacks the information of the true dynamics in the transition. In addition, stochastic effects can induce early/late onset of the bifurcating behavior, which then leads to inaccurate prediction of the observed bifurcation point in the deterministic model. Applications and comparisons of the deterministic and discrete stochastic analysis applied to the Schlögl model and a genetic toggle switch model demonstrated the importance of applying the appropriate sensitivity analysis according to the dynamics of the process.

Acknowledgments

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