An efficient and unbiased method for sensitivity analysis of stochastic reaction networks

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Abstract

We consider the problem of estimating parameter sensitivity for Markovian models of reaction networks. Sensitivity values measure the responsiveness of an output to the model parameters. They help in analyzing the network, understanding its robustness properties and identifying the important reactions for a specific output. Sensitivity values are commonly estimated using methods that perform finite-difference computations along with Monte Carlo simulations of the reaction dynamics. These methods are computationally efficient and easy to implement, but they produce a biased estimate which can be unreliable for certain applications. Moreover the size of the bias is generally unknown and hence the accuracy of these methods cannot be easily determined. There also exist unbiased schemes for sensitivity estimation but these schemes can be computationally infeasible, even for simple networks. Our goal in this paper is to present a new method for sensitivity estimation, which combines the computational efficiency of finite-difference methods with the accuracy of unbiased schemes. Our method is easy to implement and it relies on an exact representation of parameter sensitivity that we recently proved in an earlier paper. Through examples we demonstrate that the proposed method can outperform the existing methods, both biased and unbiased, in many situations.

Keywords: parameter sensitivity; reaction networks; Markov process; finite-difference schemes; random time-change representation; common reaction path (CRP); coupled finite-difference (CFD); Girsanov method.

Mathematical Subject Classification (2010): 60J22; 60J27; 60H35; 65C05.

1 Introduction

Reaction networks are frequently encountered in several scientific disciplines, such as, Chemistry [6], Systems Biology [17, 22], Epidemiology [15], Ecology [2] and Pharmacology [3]. It is well-known that when the population sizes of the reacting species are small, then a deterministic formulation of the reaction dynamics is inadequate in understanding many important properties of the system (see [5, 16]). Hence stochastic models are necessary and the most prominent class of such models is where the reaction dynamics is described by a continuous time Markov chain. Our paper is concerned with sensitivity analysis of these Markovian models of reaction networks.

Generally, reaction networks involve many kinetic parameters that influence their dynamics. With sensitivity analysis one can measure the receptiveness of an outcome with respect to small changes in parameter values. These sensitivity values give insights about network design and its robustness properties [21]. They also help in identifying the important reactions for a given output, estimating the model parameters and in fine-tuning the system’s behaviour [8]. The existing literature contains many methods for sensitivity analysis of stochastic reaction networks, but all these methods have certain drawbacks. They either introduce a bias in the sensitivity estimate [13, 19, 20, 1] or the associated estimator can have large variances [18] or the
method becomes impractical for large networks [14]. Due to these reasons, the search for better methods for sensitivity analysis of stochastic reaction networks is still an active research problem.

We now formally describe a stochastic reaction network consisting of \( d \) species \( S_1, \ldots, S_d \). Under the well-stirred assumption [11], the state of the system at any time is given by a vector in \( \mathbb{N}_d^0 \), where \( \mathbb{N}_d^0 \) is the set of non-negative integers. When the state is \( x = (x_1, \ldots, x_d) \) then the population size corresponding to species \( S_i \) is \( x_i \). The state evolves as the species interact through \( K \) reaction channels. If the state is \( x \), the \( k \)-th reaction fires at rate \( \lambda_k(x) \) and it displaces the state by the stoichiometric vector \( \zeta_k \in \mathbb{Z}^d \). Here \( \lambda_k \) is called the propensity function for the \( k \)-th reaction. We can represent the reaction dynamics by a continuous time Markov chain and the distribution of this process evolves according to the chemical master equation [11] which is quite difficult to solve except in some restrictive cases. Fortunately, the sample paths of this process can be easily simulated using Monte Carlo procedures such as Gillespie’s stochastic simulation algorithm (SSA) or its variants [11, 10].

Suppose that the propensity functions of the reaction network depend on a scalar parameter \( \theta \). Hence when the state is \( x \), the \( k \)-th reaction fires at rate \( \lambda_k(x, \theta) \). Let \( (X_\theta(t))_{t \geq 0} \) denote the Markov process representing the reaction dynamics. For a function \( f : \mathbb{N}_d^0 \rightarrow \mathbb{R} \) and an observation time \( T \geq 0 \), our output of interest is \( f(X_\theta(T)) \). We would like to determine how much the expected value of this output changes with infinitesimal changes in the parameter \( \theta \). In other words, our aim is to compute

\[
S_\theta(f, T) = \frac{\partial}{\partial \theta} \mathbb{E}(f(X_\theta(T))) .
\]

Since the mapping \( \theta \mapsto \mathbb{E}(f(X_\theta(T))) \) is generally unknown, it is difficult to evaluate \( S_\theta(f, T) \) directly. Therefore we need to estimate this quantity using simulations of the process \( X_\theta \). For this purpose, many methods use a finite-difference scheme such as

\[
S_{\theta,h}(f, T) = \frac{1}{h} \mathbb{E}(f(X_{\theta+h}(T)) - f(X_\theta(T)))
\]

for a small \( h \). These methods reduce the variance of the associated estimator by coupling the processes \( X_\theta \) and \( X_{\theta+h} \) in an intelligent way. Three such couplings are: Common Reaction Numbers (CRN) (see [19]), Common Reaction Paths (CRP) (see [19]) and Coupled finite-differences (CFD) (see [1]). The two best performing finite-difference schemes are CRP and CFD and we shall discuss them in greater detail in Section 2.1. It is immediate that a finite-difference scheme produces a biased estimate of the true sensitivity value \( S_{\theta,h}(f, T) \). This problem of bias is compounded by the fact that in most cases, the size and even the sign of the bias is unknown, thereby casting a doubt over the estimated sensitivity values. The magnitude of the bias must be proportional to \( h \), but it can still be significant for a small \( h \) (see Section 4). One can reduce the bias by decreasing \( h \), but as \( h \) gets smaller, the variance of the finite-difference estimator gets larger, making these schemes inefficient in comparison to the unbiased methods. This point is highlighted by the examples in Section 4.

We now discuss the unbiased methods for sensitivity analysis of stochastic reaction networks. The first such method was given by Plyasunov and Arkin [18] and it relies on the Girsanov measure transformation. Hence we refer to it as the Girsanov method in this paper. In this method the sensitivity value \( S_\theta(f, T) \) is expressed as

\[
S_\theta(f, T) = \mathbb{E}(s_\theta(f, T)) ,
\]

where \( s_\theta(f, t) \) is a random variable whose realizations can be easily obtained by simulating paths of the process \( X_\theta \) in the time interval \([0, T]\). The Girsanov method is easy to implement, and being unbiased, one is guaranteed to converge to the right value \( S_\theta(f, T) \) as the sample size tends to infinity. However in many situations, the estimator associated with this method has a very high variance, making it necessary to generate an extremely large number of samples to obtain a statistically accurate estimate (see the examples in [19, 20, 1]). One such situation arises when the sensitive parameter \( \theta \) is a reaction rate constant with a small size (see [14]). To remedy this problem of high estimator variances, we proposed another unbiased scheme in [14], which is based on a different sensitivity formula of the form (1.3). In this formula, the expression for the random variable \( s_\theta(f, T) \) is derived using the random time-change representation of Kurtz (see Chapter 7 in [7]). Unfortunately this expression is such that realizations of the random variable \( s_\theta(f, T) \) cannot be
easily computed from the paths of the process \( X_\theta \) as the expression involves several expectations of functions of the underlying Markov process at various times and various initial states. If all these expectations are estimated \textit{serially} using independent paths then the problem becomes computationally intractable. Hence we devised a scheme in [14], called the \textit{Auxiliary Path Algorithm} (APA), to estimate all these expectations in \textit{parallel} using a fixed number of \textit{auxiliary} paths. The implementation of APA is quite difficult and the memory requirements are very high because one needs to store the paths and dynamically maintain a large table to estimate the relevant quantities. These reasons make APA impractical for large networks and also for large observation times \( T \). However, in spite of these difficulties, we showed in [14] that APA can be far more efficient than the Girsanov method, in examples where sensitivity is computed with respect to a small reaction rate constant.

The above discussion suggests that all the existing methods for sensitivity analysis, both biased and unbiased, have certain drawbacks. Motivated by this issue, we develop a new method for sensitivity estimation in this paper which is unbiased, easy to implement, has low memory requirements and is more versatile than the existing unbiased schemes. We use the main result in [14], to construct another random variable \( s_\theta(f,T) \) such that (1.3) holds. We then provide a simple scheme, called the \textit{Poisson Path Algorithm} (PPA), to obtain realizations of \( s_\theta(f,T) \) and this gives us a method to obtain unbiased estimates of parameter sensitivities for stochastic reaction networks. Similar to APA, PPA also requires estimation of certain quantities using auxiliary paths, but the number of these quantities can be kept so low, that they can be estimated serially using independent paths. Hence PPA does not require any storage of paths or the dynamic maintenance of a large table as in APA. As a result, memory requirements are low, the implementation is easier, and PPA works well for large networks and for large observation times \( T \). In Section 4 we consider many examples to compare the performance of PPA with the Girsanov method, CFD and CRP. We find that PPA is usually far more efficient than the Girsanov method. Perhaps surprisingly, in many situations PPA can also outperform the finite-difference schemes (CRP and CRN) if we impose the restriction that the bias is small. This makes PPA an attractive method for sensitivity analysis because one can efficiently obtain sensitivity estimates and not have to worry about the (unknown) bias caused by finite-difference approximations.

This paper is organized as follows. In Section 2 we provide the relevant mathematical background and also discuss the existing schemes for sensitivity analysis in greater detail. We also present our main result which shows that for a suitably defined \( s_\theta(f,T) \), the relation (1.3) is satisfied. In Section 3 we describe PPA which is a simple method to obtain realizations of the random variable \( s_\theta(f,T) \). In Section 4 we consider many examples to illustrate the efficiency of PPA and compare its performance with other methods. Finally in Section 5 we conclude and discuss future research directions.

## 2 Preliminaries

Recall the description of the reaction network from the previous section and suppose that the propensity functions depend on a real-valued parameter \( \theta \). We can model the reaction dynamics by a continuous time Markov process whose generator\(^1\) is given by

\[
A_\theta f(x) = \sum_{k=1}^{K} \lambda_k(x, \theta) \Delta \zeta_k f(x),
\]

where \( f : \mathbb{N}_0^d \rightarrow \mathbb{R} \) is any bounded function and \( \Delta \zeta f(x) = f(x + \zeta) - f(x) \). Under some mild conditions on the propensity functions (see Condition 2.1 in [14]), a Markov process \((X_\theta(t))_{t \geq 0}\) with generator \( A_\theta \) and any initial state \( x_0 \), exists uniquely. The random time-change representation of Kurtz (see Chapter 7 in [7]) shows that this process can be expressed as

\[
X_\theta(t) = x_0 + \sum_{k=1}^{K} Y_k \left( \int_0^t \lambda_k(X_\theta(s), \theta) ds \right) \zeta_k,
\]  

(2.4)

where \( \{Y_k : k = 1, ..., K\} \) is a family of independent unit rate Poisson processes.

\(^1\)The generator of a Markov process is an operator which specifies the rate of change of the distribution of the process. See Chapter 4 in [7] for more details.
In this paper we are interested in computing the sensitivity value \( S_\theta(f, T) \) defined by (1.1). Suppose we can express the sensitivity value as (1.3) for some random variable \( s_\theta(f, T) \). If we are able to generate \( N \) independent samples \( s_\theta^{(1)}(f, T), \ldots, s_\theta^{(N)}(f, T) \) from the distribution of \( s_\theta(f, T) \), then \( S_\theta(f, T) \) can be estimated as

\[
\tilde{S}_\theta(f, T) = \frac{1}{N} \sum_{i=1}^{N} s_\theta^{(i)}(f, T).
\]  

(2.5)

The variance of this estimator is

\[
\text{Var}(\tilde{S}_\theta(f, T)) = \text{Var}\left( \frac{1}{N} \sum_{i=1}^{N} s_\theta^{(i)}(f, T) \right) = \frac{1}{N} \text{Var}(s_\theta(f, T)).
\]  

(2.6)

Generally \( \text{Var}(s_\theta(f, T)) \) is unknown, but we can replace it by the sample variance

\[
\hat{\sigma}(s_\theta(f, T)) = \frac{1}{N-1} \sum_{i=1}^{N} (s_\theta^{(i)}(f, T) - \tilde{S}_\theta(f, T))^2
\]

to evaluate \( \text{Var}(\tilde{S}_\theta(f, T)) \). Due to the Central Limit Theorem, for large values of \( N \), the distribution of \( \tilde{S}_\theta(f, T) \) is approximately normal with variance given by (2.6). Hence the half-length of the 95% confidence interval for the above estimator can be computed as

\[
l = 1.96 \sqrt{\text{Var}(\tilde{S}_\theta(f, T))} = \frac{1.96}{\sqrt{N(N-1)}} \sum_{i=1}^{N} (s_\theta^{(i)}(f, T) - \tilde{S}_\theta(f, T))^2.
\]  

(2.7)

Such a confidence interval can be used to specify the statistical accuracy of the estimator. Observe that if one wants to estimate the sensitivity value \( S_\theta(f, T) \) within a certain confidence interval, then the number of samples needed for this purpose is directly proportional to the variance of \( s_\theta(f, T) \).

In finite-difference schemes, instead of \( S_\theta(f, T) \) one estimates a finite-difference \( S_{\theta,h}(f, T) \) of the form (1.2) which can be written as \( S_{\theta,h}(f, T) = \mathbb{E}(s_{\theta,h}(f, T)) \) for

\[
s_{\theta,h}(f, T) = \frac{f(X_{\theta+h}(T)) - f(X_\theta(T))}{h}.
\]  

(2.8)

Here the Markov processes \( X_\theta \) and \( X_{\theta+h} \) are defined on the same probability space and they have generators \( k_\theta \) and \( k_{\theta+h} \) respectively. Note that in this case, the number of samples needed to obtain a desired level of statistical accuracy is proportional to the variance of \( s_{\theta,h}(f, T) \).

### 2.1 Finite-difference schemes

The main idea behind the various finite-difference schemes is that by coupling the processes \( X_\theta \) and \( X_{\theta+h} \), one can increase the covariance between \( f(X_{\theta+h}(T)) \) and \( f(X_\theta(T)) \), thereby reducing the variance of \( s_{\theta,h}(f, T) \) and making the estimation procedure more efficient. As mentioned in the introduction, three such couplings suggested by the existing literature are: Common Reaction Numbers (CRN) (see [19]), Common Reaction Paths (CRP) (see [19]) and Coupled finite-differences (CFD) (see [1]). Among these we only consider the two best performing schemes, CRP and CFD, in this paper.

In CRP the processes \( X_\theta \) and \( X_{\theta+h} \) are coupled by their random time-change representations according to

\[
X_\theta(t) = x_0 + \sum_{k=1}^{K} Y_k \left( \int_0^t \lambda_k(X_\theta(s), \theta) ds \right) \zeta_k \quad \text{and} \quad X_{\theta+h}(t) = x_0 + \sum_{k=1}^{K} Y_k \left( \int_0^t \lambda_k(X_{\theta+h}(s), \theta + h) ds \right) \zeta_k,
\]

where \( \{Y_k : k = 1, \ldots, K\} \) is a family of independent unit rate Poisson processes. Note that these Poisson processes are same for both processes \( X_\theta \) and \( X_{\theta+h} \), indicating that their reaction paths are the same.
In CFD the processes \(X_\theta\) and \(X_{\theta+h}\) are coupled by their random time-change representations according to

\[
X_\theta(t) = x_0 + \sum_{k=1}^{K} Y_k \left( \int_0^t \lambda_k(X_\theta(s), \theta) \land \lambda_k(X_{\theta+h}(s), \theta + h) ds \right) \zeta_k
\]

\[
+ \sum_{k=1}^{K} Y_k^{(1)} \left( \int_0^t [\lambda_k(X_\theta(s), \theta) - \lambda_k(X_\theta(s), \theta) \land \lambda_k(X_{\theta+h}(s), \theta + h)] ds \right) \zeta_k
\]

and \(X_{\theta+h}(t) = x_0 + \sum_{k=1}^{K} Y_k \left( \int_0^t \lambda_k(X_\theta(s), \theta) \land \lambda_k(X_{\theta+h}(s), \theta + h) ds \right) \zeta_k
\]

\[
+ \sum_{k=1}^{K} Y_k^{(2)} \left( \int_0^t [\lambda_k(X_{\theta+h}(s), \theta + h) - \lambda_k(X_\theta(s), \theta) \land \lambda_k(X_{\theta+h}(s), \theta + h)] ds \right) \zeta_k,
\]

where \(a \land b = \min\{a, b\}\) and \(\{Y_k, Y_k^{(1)}, Y_k^{(2)} : k = 1, ..., K\}\) is again a family of independent unit rate Poisson processes. Under this coupling, the processes \(X_\theta\) and \(X_{\theta+h}\) have the same state until the first time the counting process corresponding to \(Y_k^{(1)}\) or \(Y_k^{(2)}\) fires for some \(k\). The probability that this separation time will come before \(T\) is proportional to \(h\), which is usually a small number. Hence for the majority of simulation runs, the processes \(X_\theta\) and \(X_{\theta+h}\) are together for the whole time interval \([0, T]\), suggesting that they are strongly coupled.

Note that both CRP and CRN are estimating the same quantity \(S_{\theta,h}(f, T)\) given by \((2.2)\) and hence they both suffer from the same bias \(|S_{\theta,h}(f, T) - S_\theta(f, T)|\). The only difference between these two methods is in the coupling of the processes \(X_\theta\) and \(X_{\theta+h}\), which alters the variance of \(s_{\theta,h}(f, T)\) \((2.8)\). For a given example, the method with a lower variance will be more efficient as it will require fewer number of samples \((N)\) to achieve the desired statistical accuracy.

For any finite-difference scheme, one can show that the bias \(|S_{\theta,h}(f, T) - S_\theta(f, T)|\) is proportional to \(h\) while \(\text{Var}(s_{\theta,h}(f, T))\) is proportional to \(1/h\). Therefore by making \(h\) smaller we may reduce the bias but we will have to pay a computational cost by generating a large number of samples for the required estimation. This trade-off between bias and computational efficiency is the major drawback of finite-difference schemes as one generally does not know the right value of \(h\) for which \(S_{\theta,h}(f, T)\) is close enough to \(S_\theta(f, T)\), while at the same time the variance of \(\text{Var}(s_{\theta,h}(f, T))\) is not too large. The examples in Section 4 emphasize this issue.

### 2.2 Unbiased schemes

Unbiased schemes are desirable for sensitivity estimation because one does not have to worry about the bias and the accuracy of the estimate can be improved by simply increasing the number of samples. The Girsanov method is the first such unbiased scheme (see [18] and [24]). Recall the random time-change representation \((2.4)\) of the process \((X_\theta(t))_{t \geq 0}\). In the Girsanov method, we express \(S_\theta(f, T)\) as \((1.3)\) where

\[
s_\theta(f, T) = f(X_\theta(T)) \sum_{k=1}^{K} \left( \int_0^T \frac{1}{\lambda_k(X_\theta(t), \theta)} \frac{\partial \lambda_k(X_\theta(t), \theta)}{\partial \theta} R_k(dt) - \int_0^T \frac{\partial \lambda_k(X_{\theta+h}(t), \theta)}{\partial \theta} dt \right)
\]

and \((R_k(t))_{t \geq 0}\) is the counting process given by

\[
R_k(t) = Y_k \left( \int_0^t \lambda_k(X_\theta(s), \theta) ds \right).
\]

In \((2.9)\), \(R_k(dt) = 1\) if and only if the \(k\)-th fires at time \(t\). For any other \(t\), \(R_k(dt) = 0\). Hence we can write

\[
\int_0^T \frac{1}{\lambda_k(X_\theta(t), \theta)} \frac{\partial \lambda_k(X_\theta(t), \theta)}{\partial \theta} R_k(dt) = \sum_{j=1}^{n_k} \frac{1}{\lambda_k(X_{\theta+h}(t_j^{(k)}), \theta)} \frac{\partial \lambda_k(X_{\theta+h}(t_j^{(k)}), \theta)}{\partial \theta},
\]
if the $k$-th reaction fires at times $t_1^{(k)}, \ldots, t_n^{(k)}$ in the time interval $[0, T]$.

The Girsanov method is simple to implement because realizations of the random variable $s_\theta(f, T)$ can be easily generated by simulating the paths of the process $X_\theta$ until time $T$. However, as mentioned before, the variance of $s_\theta(f, T)$ can be very high (see [19, 20, 1]), which is a serious problem as it implies that a large number of samples are needed to produce statistically accurate estimates. Since simulations of the process $X_\theta$ can be quite cumbersome, generating a large sample can take an enormous amount of time.

Now consider the common situation where we have mass-action kinetics and $\theta$ is the rate constant of reaction $k_0$. In this case, $\lambda_{k_0}$ has the form $\lambda_{k_0}(x, \theta) = \theta \lambda'_0(x)$ and for every $k \neq k_0$, $\lambda_k$ does not depend on $\theta$. Therefore

$$\frac{\partial \lambda_k(x, \theta)}{\partial \theta} = \begin{cases} \frac{1}{\theta} \lambda_{k_0}(x, \theta) & \text{if } k = k_0 \\ 0 & \text{otherwise} \end{cases}$$

and hence the formula (2.9) for $s_\theta(f, T)$ simplifies to

$$s_\theta(f, T) = \frac{1}{\theta} f(X_\theta(T)) \left( N_{\theta}^{k_0}(T) - \int_0^T \lambda_{k_0}(X_\theta(t), \theta) dt \right),$$  \hspace{1cm} (2.10)

where $N_{\theta}^{k_0}(T)$ is the number of times the reaction $k_0$ fires in the time interval $[0, T]$. This formula clearly shows that the Girsanov method cannot be used to estimate the sensitivity value at $\theta = 0$ even though $S_\theta(f, T)$ (see (1.1)) is well-defined. This is a big disadvantage since the sensitivity value at $\theta = 0$ is useful for understanding the network design as it informs us whether the presence or absence of reaction $k_0$ influences the output or not. Unfortunately the problem with the Girsanov method is not just limited to $\theta = 0$. Even for $\theta$ close to 0, the variance of $s_\theta(f, T)$ can be very high, rendering this method practically infeasible (see [14]). This is again a serious drawback as reaction rate constants with small values are frequently encountered in systems biology and other areas.

These issues with the Girsanov method severely restrict its use and also highlight the need for new unbiased schemes for sensitivity analysis. We provided another such scheme in our recent paper [14]. This scheme is based on another sensitivity formula of the form (1.3) which was proved using the random time-change representation. To present this formula we need to define certain quantities. Let $(X_\theta(t))_{t \geq 0}$ be a Markov process with generator $A_\theta$. For any $f : \mathbb{N}_0^d \to \mathbb{R}$, $t \geq 0$ and $x \in \mathbb{N}_0^d$ define

$$\Psi_\theta(x, f, t) = \mathbb{E}(f(X_\theta(t)) | X_\theta(0) = x),$$

and for any $k = 1, \ldots, K$ let

$$D_\theta(x, f, t, k) = \Psi_\theta(x + \zeta_k, f, t) - \Psi_\theta(x, f, t).$$  \hspace{1cm} (2.11)

Define $\lambda_0(x, \theta) = \sum_{k=1}^K \lambda_k(x, \theta)$ and let $\sigma_0, \sigma_1, \sigma_2$ denote the successive jump times\footnote{We define $\sigma_0 = 0$ for convenience} of the process $X_\theta$. Theorem 2.3 in [14] shows that $S_\theta(f, T)$ satisfies (1.3) with

$$s_\theta(f, T) = \sum_{k=1}^K \left( \int_0^T \frac{\partial \lambda_k(X_\theta(t), \theta)}{\partial \theta} \Delta_{\zeta_k} f(X_\theta(t)) dt + \sum_{i=0, \sigma_i < T}^{\infty} \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} R_\theta(X_\theta(\sigma_i), f, T - \sigma_i, k) \right),$$  \hspace{1cm} (2.12)

where

$$R_\theta(x, f, t, k) = \int_0^t (D_\theta(x, f, s, k) - \Delta_{\zeta_k} f(x)) e^{-\lambda_0(x, \theta) (t-s)} ds.$$  \hspace{1cm} (2.13)

From (2.12) one can see that realizations of the random variable $s_\theta(f, T)$ cannot be simply evaluated from the paths of the process $X_\theta$ in the time interval $[0, T]$. This is because, in general, one does not have an explicit formula for the function $R_\theta$. To overcome this problem, one needs to estimate all the quantities of the form $R_\theta(x, f, t, k)$ that appear in (2.12). However the number of these quantities is proportional to
the number of jumps of the process before time $T$, which can be quite high even for small networks. If we estimate each of these quantities *serially*, as and when they appear, using a collection of independently generated paths of the process $X_\theta$, then the problem becomes computationally intractable for most examples of interest. In [14] we devised a scheme, called the Auxiliary Path Algorithm (APA), to estimate all these quantities in *parallel* by generating a fixed number of auxiliary paths in addition to the main path. APA stores information about all the required quantities in a big Hashtable and tracks the states visited by the auxiliary paths to estimate those quantities. Due to all the necessary book-keeping, APA is hard to implement and it also requires a lot of memory. In fact the space and time complexity of APA scales linearly with the number of jumps in the time interval $[0,T]$ and this makes APA practically unusable for large networks or for large values of observation time $T$. Moreover APA only works well if the stochastic dynamics visits the same states again and again, which may not be generally true.

As mentioned above, the main difficulty in using expression (2.12) for sensitivity estimation is that one needs to estimate a quantity like $R_\theta(x,f,t,k)$ at each jump time $\sigma_i$ that falls below $T$. If one can modify this expression in such a way that only a small fraction of these quantities require estimation, then it can lead to an efficient method for sensitivity analysis. We exploit this idea in this paper. By adding extra randomness to the random variable $s_\theta(f,T)$ (2.12), we construct another random variable $\hat{s}_\theta(f,T)$, which has the same expectation as $s_\theta(f,T)$

$$\mathbb{E}(s_\theta(f,T)) = \mathbb{E}(\hat{s}_\theta(f,T)), \quad (2.14)$$

even though its distribution may be different. We then show that realizations of the random variable $\hat{s}_\theta(f,T)$ can be easily obtained through a simple procedure. This gives us a new method for unbiased parameter sensitivity estimation for stochastic reaction networks.

### 2.3 Construction of $\hat{s}_\theta(f,T)$

We now describe the construction of the random variable $\hat{s}_\theta(f,T)$ introduced in the previous section. Let $(X_\theta(t))_{t \geq 0}$ be the Markov process with generator $A_\theta$ and initial state $x_0$. Let $\sigma_0, \sigma_1, \ldots$ denote the successive jump times of this process. The total number of jumps until time $T$ is given by the random variable

$$\eta = \max\{i \geq 0 : \sigma_i < T\}. \quad (2.15)$$

Note that for any $T > 0$ we have $\eta \geq 1$ because $\sigma_0 = 0$. If the Markov process $X_\theta$ reaches a state $x$ for which $\lambda_0(x,\theta) = 0$, then $x$ is an absorbing state and the process stays in $x$ forever. From (2.15), it is immediate that for any non-negative integer $i < \eta$, $X_\theta(\sigma_i)$ cannot be an absorbing state. Let $\alpha$ indicate if the final state $X_\theta(\sigma_\eta)$ is absorbing

$$\alpha = \left\{ \begin{array}{ll} 1 & \text{if } \lambda_0(X_\theta(\sigma_\eta),\theta) = 0 \\ 0 & \text{otherwise} \end{array} \right\}. \quad (2.16)$$

For each $i = 0,\ldots, (\eta - \alpha)$ let $\gamma_i$ be an independent exponentially distributed random variable with rate $\lambda_0(X_\theta(\sigma_i),\theta)$ and define

$$\Gamma_i = \left\{ \begin{array}{ll} 1 & \text{if } \gamma_i < (T - \sigma_i) \\ 0 & \text{otherwise} \end{array} \right\}. \quad (2.17)$$

For each $i = 0,\ldots, (\eta - \alpha)$ and $k = 1,\ldots, K$ let $\beta_{ki}$ be given by

$$\beta_{ki} = \text{Sign}\left( \frac{\partial \lambda_k(X_\theta(\sigma_i),\theta)}{\partial \theta} \right) \text{ where } \text{Sign}(x) = \left\{ \begin{array}{ll} 1 & \text{if } x > 0 \\ -1 & \text{if } x < 0 \\ 0 & \text{if } x = 0 \end{array} \right\}. \quad (2.18)$$

Fix a normalizing constant $c > 0$. The choice of $c$ and its role will be explained later in the section. If $\beta_{ki} \neq 0$ and $\Gamma_i = 1$, then let $\rho_{ki}^{(c)}$ be an independent $\mathbb{N}_0$-valued random variable whose distribution is Poisson with parameter

$$\frac{c}{\lambda_0(X_\theta(\sigma_i),\theta)} \left| \frac{\partial \lambda_k(X_\theta(\sigma_i),\theta)}{\partial \theta} \right|. \quad (2.16)$$
Here the denominator \( \lambda_0(X_\theta(x), \theta) \) is non-zero because for \( i \leq (\eta - \alpha) \) the state \( X_\theta(x_i) \) cannot be absorbing. On the event \( \{ \beta_{ki} \neq 0, \Gamma_i = 1 \) and \( \rho^{(c)}_{ki} > 0 \} \) we define another random variable as

\[
\hat{D}_{ki} = f(Z_1(T - \sigma_i - \gamma_i)) - f(Z_2(T - \sigma_i - \gamma_i)),
\]

(2.17)

where \( (Z_1(t))_{t \geq 0} \) and \( (Z_2(t))_{t \geq 0} \) are two processes which are coupled by the following random time-change representations:

\[
Z_1(t) = (X_\theta(x_i) + \zeta_k) + \sum_{k=1}^{K} \tilde{Y}_k \left( \int_0^t \lambda_k(Z_1(s), \theta) - \lambda_k(Z_2(s), \theta) \, ds \right) \zeta_k
+ \sum_{k=1}^{K} \tilde{Y}_k^{(1)} \left( \int_0^t \lambda_k(Z_1(s), \theta) \, ds \right) \zeta_k
\]

and \( Z_2(t) = X_\theta(x_i) + \sum_{k=1}^{K} \tilde{Y}_k \left( \int_0^t \lambda_k(Z_2(s), \theta) \, ds \right) \zeta_k
+ \sum_{k=1}^{K} \tilde{Y}_k^{(2)} \left( \int_0^t \lambda_k(Z_2(s), \theta) - \lambda_k(Z_1(s), \theta) \, ds \right) \zeta_k,
\]

where \( \{ \tilde{Y}_k, \tilde{Y}_k^{(1)}, \tilde{Y}_k^{(2)} : k = 1, \ldots, K \} \) is an independent family of unit rate Poisson processes. This coupling is similar to the coupling used by the finite-difference scheme CFD (see Section 2.1). Note that \( (Z_1(t))_{t \geq 0} \) and \( (Z_2(t))_{t \geq 0} \) are Markov processes with generator \( \Lambda_\theta \) and initial states \( (X_\theta(x_i) + \zeta_k) \) and \( X_\theta(x_i) \) respectively. Therefore

\[
E \left( \hat{D}_{ki} \bigg| T - \sigma_i - \gamma_i, X_\theta(x_i) \right) = \Psi_\theta(X_\theta(x_i) + \zeta_k, f, T - \sigma_i - \gamma_i) - \Psi_\theta(X_\theta(x_i), f, T - \sigma_i - \gamma_i)
= D_\theta(x_\theta(x_i), f, T - \sigma_i - \gamma_i, k),
\]

(2.18)

where \( D_\theta \) is defined by (2.11). In other words, given \( T - \sigma_i - \gamma_i = t \) and \( X_\theta(x_i) = x \), the mean of the random variable \( \hat{D}_{ki} \) is just \( D_\theta(x, f, t, k) \). The above coupling between \( (Z_1(t))_{t \geq 0} \) and \( (Z_2(t))_{t \geq 0} \) makes them strongly correlated, thereby lowering the variance of the difference \( \hat{D}_{ki} = f(Z_1(t)) - f(Z_2(t)) \). This strong correlation is evident from the fact that if \( Z_1(s) = Z_2(s) \) for some \( s \geq 0 \) then \( Z_1(u) = Z_2(u) \) for all \( u \geq s \). Finally, if the last state \( X_\theta(x_\eta) \) is absorbing (that is, \( \alpha = 1 \) and \( \partial \lambda_k(X_\theta(x_\eta), \theta) \) is non-zero then we define another random variable \( \hat{I}_{k\eta} \) as

\[
\hat{I}_{k\eta} = \int_0^{T-\sigma_\eta} f(Z(s)) \, ds,
\]

(2.19)

where \( (Z(t))_{t \geq 0} \) is an independent Markov process with generator \( \Lambda_\theta \) and initial state \( X_\theta(x_\eta) + \zeta_k \). Note that

\[
E \left( \hat{I}_{k\eta} \bigg| X_\theta(x_\eta), T - \sigma_\eta \right) = \int_0^{T-\sigma_\eta} \Psi_\theta(X_\theta(x_\eta) + \zeta_k, f, s) \, ds.
\]

(2.20)

We are now ready to provide an expression for \( \hat{\theta}_\theta(f, T) \). Let

\[
\Delta t_i = \begin{cases} 
\{ (\sigma_{i+1} - \sigma_i) & \text{for } i = 0, \ldots, \eta - 1 \\
(T - \sigma_\eta) & \text{for } i = \eta 
\end{cases}
\]

and define

\[
\hat{\theta}_\theta(f, T) = \sum_{k=1}^{K} \sum_{i=0}^{\eta-1} \left[ \frac{\partial \lambda_k(X_\theta(x_i), \theta)}{\partial \theta} \Delta t_i f(X_\theta(x_i)) \left( \Delta t_i - \frac{\Gamma_i}{\lambda_\theta(X_\theta(x_i), \theta)} \right) + \frac{1}{c} \beta_{ki} \Gamma_i \rho^{(c)}_{ki} \hat{D}_{ki} \right] + \alpha \sum_{k=1}^{K} \left[ \frac{\partial \lambda_k(X_\theta(x_\eta), \theta)}{\partial \theta} \left( \hat{I}_{k\eta} - (T - \sigma_\eta) f(X_\theta(x_\eta)) \right) \right].
\]

(2.21)

The next proposition proves relation (2.14).
Proposition 2.1 Let \((X_\theta(t))_{t \geq 0}\) be the Markov process with initial state \(x_0\), generator \(k_\theta\) and jump times \(\sigma_0, \sigma_1, \ldots\). Let \(s_\theta(f, T)\) and \(\tilde{s}_\theta(f, T)\) be the random variables given by (2.12) and (2.21) respectively. Then (2.14) is satisfied for any \(f : \mathbb{N}_0^d \to \mathbb{R}\) and \(T \geq 0\).

Proof. Let \(\{F_t\}_{t \geq 0}\) be the family of filtrations generated by \((X_\theta(t))_{t \geq 0}\). In other words, \(F_t\) is the sigma field containing information about the process \(X_\theta\) until time \(t\). Note that the random variables \(\eta\) and \(\alpha\) are measurable with respect to \(F_T\). Moreover for every \(i = 1, \ldots, \eta\), the random variables \(\sigma_i, \Delta t_i, X_\theta(\sigma_i)\) and \(\beta_{ki}\) are also \(F_T\)-measurable.

Given \(X_\theta(\sigma_i)\), the random variable \(\gamma_i\) is independent of \(F_T\) and it is exponentially distributed with parameter \(\lambda_0(X_\theta(\sigma_i), \theta)\). This implies that

\[
\mathbb{E}\left(\frac{\Gamma_i}{\lambda_0(X_\theta(\sigma_i), \theta)} | F_T\right) = \frac{1}{\lambda_0(X_\theta(\sigma_i), \theta)} \mathbb{P}(\gamma_i < T - \sigma_i | F_T) = \int_0^{T - \sigma_i} e^{-\lambda_0(X_\theta(\sigma_i), \theta) s} ds,
\]

and from (2.18) we obtain

\[
\mathbb{E}\left(\Gamma_i, \tilde{D}_{ki} | F_T\right) = \int_0^{T - \sigma_i} \lambda_0(X_\theta(\sigma_i), \theta)D_\theta(X_\theta(\sigma_i), f, T - \sigma_i - s, k)e^{-\lambda_0(X_\theta(\sigma_i), \theta) s} ds.
\]

Given \(X_\theta(\sigma_i)\), \(\rho^{(c)}_{ki}\) is a Poisson random variable independent of \(F_T\) and hence

\[
\mathbb{E}\left(\rho^{(c)}_{ki} | F_T\right) = \frac{c}{\lambda_0(X_\theta(\sigma_i), \theta)} \left| \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} \right|.
\]

Observe that \(\rho^{(c)}_{ki}\) and \(\Gamma_i, \tilde{D}_{ki}\) are conditionally independent given \(F_T\). Combining (2.23) and (2.24) we get

\[
\mathbb{E}\left(\frac{1}{c} \beta_{ki} \Gamma_i \rho^{(c)}_{ki} \tilde{D}_{ki} | F_T\right) = \left(\int_0^{T - \sigma_i} \lambda_0(X_\theta(\sigma_i), \theta)D_\theta(X_\theta(\sigma_i), f, T - \sigma_i - s, k)e^{-\lambda_0(X_\theta(\sigma_i), \theta) s} ds\right)
\]

\[
\times \left(\left| \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} \right| \int_0^{T - \sigma_i} D_\theta(X_\theta(\sigma_i), f, T - \sigma_i - s, k)e^{-\lambda_0(X_\theta(\sigma_i), \theta) s} ds\right)
\]

\[
= \left(\left| \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} \right| \int_0^{T - \sigma_i} D_\theta(X_\theta(\sigma_i), f, T - \sigma_i - s, k)e^{-\lambda_0(X_\theta(\sigma_i), \theta) s} ds\right)
\]

\[
+ \left(\frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} R_\theta(X_\theta(\sigma_i), f, T - \sigma_i, k)\right)
\]

\[
\Delta \zeta f(X_\theta(\sigma_i)) \int_0^{T - \sigma_i} e^{-\lambda_0(X_\theta(\sigma_i), \theta) s} ds,
\]

where \(R_\theta\) is defined by (2.13).

On the event \(\{\alpha = 1\}\), the state \(X_\theta(\sigma_\eta)\) is absorbing \((\lambda_0(X_\theta(\sigma_\eta), \theta) = 0)\). Hence \(\Psi_\theta(X_\theta(\sigma_\eta), f, s) = f(X_\theta(\sigma_\eta))\) for all \(s \geq 0\). From (2.20) we get

\[
\mathbb{E}\left(\tilde{I}_{\eta} | F_T\right) = \int_0^{T - \sigma_\eta} \Psi_\theta(X_\theta(\sigma_\eta) + \zeta_k, f, s) ds
\]

\[
= \int_0^{T - \sigma_\eta} D_\theta(X_\theta(\sigma_\eta), f, T - \sigma_\eta - s, k) ds + (T - \sigma_\eta)f(X_\theta(\sigma_\eta))
\]

\[
= R_\theta(X_\theta(\sigma_\eta), f, T - \sigma_\eta, k) + \Delta \zeta f(X_\theta(\sigma_\eta)) \Delta t_\eta + (T - \sigma_\eta)f(X_\theta(\sigma_\eta)).
\]

Taking conditional expectations in (2.21) yields

\[
\mathbb{E}(\tilde{s}_\theta(f, T) | F_T) = \sum_{k=1}^{K} \sum_{i=0}^{\eta - 1} \left| \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} \right| \Delta \zeta f(X_\theta(\sigma_i)) \left(\Delta t_i - \mathbb{E}\left(\frac{\Gamma_i}{\lambda_0(X_\theta(\sigma_i), \theta)} | F_T\right)\right)
\]
Using (2.22), (2.25) and (2.26) we obtain

\[ E(\hat{s}_\theta(f, T)|F_T) = s_\theta(f, T). \]

Taking expectations on both sides proves this proposition.

We mentioned before that it is difficult to obtain realizations of \( s_\theta(f, T) \) because one needs to estimate a quantity like \( R_\theta(x, f, t, k) \) at each jump time \( \sigma_i < T \), that requires simulation of new paths of the process \( X_\theta \) which is computationally expensive. Similarly for \( \hat{s}_\theta(f, T) \) (see (2.21)) we need to compute \( \hat{D}_{k_i} \) at each \( \sigma_i < T \) which also requires simulation of new paths of the process \( X_\theta \). However the main difference is that to compute \( \hat{s}_\theta(f, T) \), \( \hat{D}_{k_i} \) is only needed if the Poisson random variable \( \rho_{k_i}^{(c)} \) is strictly positive. If we can effectively control the number of positive \( \rho_{k_i}^{(c)} \)-s then we can efficiently generate realizations of \( \hat{s}_\theta(f, T) \). We later explain how this control can be achieved using the positive parameter \( c \) introduced in the definition of the random variable \( \rho_{k_i}^{(c)} \) (see (2.16)). The construction of \( \hat{s}_\theta(f, T) \) outlined above, also provides a recipe for obtaining realizations of this random variable and hence gives us a method for estimating the parameter sensitivity \( S_\theta(f, T) \). We call this method, the Poisson Path Algorithm (PPA) because at each jump time \( \sigma_i \), the crucial decision of whether new paths of the process \( X_\theta \) are needed (for \( \hat{D}_{k_i} \)) is based on the value of a Poisson random variable \( \rho_{k_i}^{(c)} \). We describe PPA in greater detail in the next section.

We now discuss how the positive parameter \( c \) can be selected. Let \( \eta_{\text{req}} \) denote the total number of positive \( \rho_{k_i}^{(c)} \)-s that appear in (2.21). This is the number of \( \hat{D}_{k_i} \)-s that are needed to obtain a realization of \( \hat{s}_\theta(f, T) \). It is immediate that \( \eta_{\text{req}} \) is bounded above by \( \rho_{\text{tot}} = \sum_{k=1}^{K} \sum_{i=0}^{\eta-\alpha} \rho_{k_i}^{(c)} \), which is a Poisson random variable with parameter \( cR_{\text{tot}} \), where

\[ R_{\text{tot}} = \sum_{k=1}^{K} \sum_{i=0}^{\eta-\alpha} \frac{1}{\lambda_0(X_\theta(\sigma_i), \theta)} \left| \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} \right|. \]

By picking a small \( c > 0 \) we can ensure that \( E(\rho_{\text{tot}}) = cE(R_{\text{tot}}) \) is small, which would also guarantee that \( \rho_{\text{tot}} \) and \( \eta_{\text{req}} \) are small. Specifically we choose a small positive integer \( M_0 \) (like 10, for instance) and set

\[ c = \frac{M_0}{E(R_{\text{tot}})}. \]

where \( E(R_{\text{tot}}) \) is estimated using \( N_0 \) simulations of the process \( X_\theta \) in the time interval \([0, T] \). The choice of \( N_0 \) is not critical and typically a small value (like 100, for example) is sufficient to provide a decent estimate.
of $E(R_{tot})$. The role of parameter $M_0$ is also not very important in determining the efficiency of PPA. If $M_0$ increases then $\eta_{req}$ increases as well, and the computational cost of generating each realization of $\hat{s}_\theta(f, T)$ becomes higher. However as $\eta_{req}$ increases the variance of $\hat{s}_\theta(f, T)$ decreases and hence a fewer number of realizations of $s_\theta(f, T)$ are required to achieve the desired statistical accuracy. These two effects usually offset each other and the overall efficiency of PPA remains relatively unaffected. Note that PPA provides unbiased estimates for the sensitivity values, regardless of the choice of $N_0$ and $M_0$.

3 The Poisson Path Algorithm (PPA)

In this section we provide full implementation details on PPA and explain how it can be used to estimate the sensitivity value $S_\theta(f, T)$ (defined by (1.1)) for some observation time $T$ and some output function $f$. Throughout this section, the function rand() is used to generate independent samples from the uniform distribution on $[0, 1]$ and $x_0$ denotes the initial state of the process $X_\theta$.

We simulate the paths of our Markov process using Gillespie’s SSA [11]. When the state of the process is $x$, the next time increment ($\Delta t$) and reaction index ($k$) is given by SSA($x$) (Algorithm 1). If the Markov process is at an absorbing state $x$, then $\lambda_0(x, \theta) = 0$ and SSA($x$) returns $(\Delta t, k) = (\infty, 0)$ implying that the process stays at $x$ forever. The first step of PPA is to find the normalization parameter $c$ from (2.28). For this we need to estimate $E(R_{tot})$ using $N_0$ simulations of the Markov process. This is done by ESTIMATE-R-TOTAL($x_0, T$) (Algorithm 2).

After we have $c$, a single realization of the random variable $\hat{s}_\theta(f, T)$ (given by (2.21)) can be computed using GENERATESAMPLE($x_0, T, c$) (Algorithm 3). This method simulates the process $X_\theta$ according to SSA and at each state $x$ and jump time $t$, the following happens:

- If $x$ is an absorbing state ($\lambda_0(x, \theta) = 0$) then $t$ is the last jump time before $T$ ($t = \sigma_\eta$). For each $k = 1, \ldots, K$ such that $\partial \lambda_k(x, \theta)/\partial \theta \neq 0$, the quantity $\hat{I}_{\kappa \eta}$ (see (2.19)) is evaluated using EVALUATEINTEGRAL($x + \zeta_k, T - t$) (Algorithm 4) and then used to update the sample value according to (2.21).

- If $x$ is not an absorbing state, then $t = \sigma_i$ for some jump time $\sigma_i$ with $i < \eta$. The exponential random variable $\gamma$ (where $\gamma = \gamma_i$ in (2.21)) is generated and for each $k = 1, \ldots, K$ such that $\partial \lambda_k(x, \theta)/\partial \theta \neq 0$, the Poisson random variable $n$ (where $n = \rho_k^{(c)}$ in (2.21)) is also generated. If $\gamma < (T-t)$ and $n > 0$ then the quantity $\hat{D}_{ki}$ (see (2.17)) is evaluated using EVALUATECOUPLEDDIFFERENCE($x, x + \zeta_k, T - t - \gamma$) (Algorithm 3) and then used to update the sample value according to (2.21). To generate a Poisson random variable with parameter $r$ we use the function GENERATEPOISSON ($r$) (Algorithm 5).

Once we have obtained $N$ realizations $s_\theta^{(1)}(f, T), \ldots, s_\theta^{(N)}(f, T)$ of the random variable $\hat{s}_\theta(f, T)$ then the sensitivity value $S_\theta(f, T)$ can be estimated by (2.5).
Algorithm 2 Computes an estimate of $\mathbb{E}(R_{\text{tot}})$ using $N_0$ simulations of the process $X_{\theta}$

1: function \textsc{Estimate-R-total}($x_0, T$)
2: Set $R = 0$
3: for $i = 1$ to $N_0$ do
4: Set $x = x_0$ and $t = 0$
5: while $t < T$ do
6: Calculate $(\Delta t, k_0) = \text{SSA}(x)$
7: if $\lambda_0(x, \theta) > 0$ then
8: for $k = 1$ to $K$ do
9: Update $R \leftarrow R + \frac{1}{\lambda_0(x, \theta)} \left| \frac{\partial \lambda_k(x, \theta)}{\partial \theta} \right|$  
10: end for
11: end if
12: Update $t \leftarrow t + \Delta t$ and $x \leftarrow x + \zeta_{k_0}$
13: end while
14: end for
15: return $R/N_0$
16: end function

Algorithm 3 Computes one realization of $\hat{s}_{\theta}(f, T)$ according to (2.21)

1: function \textsc{GenerateSample}($x_0, T, c$)
2: Set $x = x_0$, $t = 0$ and $s = 0$
3: while $t < T$ do
4: Calculate $(\Delta t, k_0) = \text{SSA}(x)$
5: Update $\Delta t \leftarrow \min\{\Delta t, T - t\}$
6: if $\lambda_0(x, \theta) > 0$ then
7: Set $\gamma = -\frac{\log(\text{rand}())}{\lambda_0(x, \theta)}$
8: end if
9: for $k = 1$ to $K$ do
10: Set $r = \left| \frac{\partial \lambda_k(x, \theta)}{\partial \theta} \right|$ and $\beta = \text{Sign} \left( \frac{\partial \lambda_k(x, \theta)}{\partial \theta} \right)$
11: if $r > 0$ then
12: if $\lambda_0(x, \theta) = 0$ then
13: Update $s \leftarrow s + \left( \frac{\partial \lambda_k(x, \theta)}{\partial \theta} \right) (\text{EvaluateIntegral}(x + \zeta_k, T - t) - (T - t)f(x))$
14: else
15: Set $n = \text{GeneratePoisson} \left( \frac{rc}{\lambda_0(x, \theta)} \right)$
16: if $\gamma < (T - t)$ then
17: Update $s \leftarrow s + \left( \frac{\partial \lambda_k(x, \theta)}{\partial \theta} \right) (f(x + \zeta_k) - f(x)) \left( \Delta t - \frac{1}{\lambda_0(x, \theta)} \right)$
18: if $n > 0$ then
19: Update $s \leftarrow s + \left( \frac{\partial n}{\partial} \right) \text{EvaluateCoupledDifference}(x, x + \zeta_k, T - t - \gamma)$
20: end if
21: else
22: Update $s \leftarrow s + \left( \frac{\partial \lambda_k(x, \theta)}{\partial \theta} \right) (f(x + \zeta_k) - f(x)) \Delta t$
23: end if
24: end if
25: end if
26: end for
27: Update $t \leftarrow t + \Delta t$ and $x \leftarrow x + \zeta_{k_0}$
28: end while
29: return $s$
30: end function
Algorithm 4 Used to evaluate $\hat{I}_{k\eta}$ given by (2.19)

1: function EvaluateIntegral($x, T_f$)
2: Set $t = 0$ and $I = 0$
3: while $t < T_f$ do
4:   Calculate $(\Delta t, k) = SSA(x)$
5:   Update $\Delta t \leftarrow \min\{\Delta t, T_f - t\}$
6:   Update $I \leftarrow I + f(x)\Delta t$
7:   Update $t \leftarrow t + \Delta t$ and $x \leftarrow x + \zeta_k$
8: end while
9: return $I$
10: end function

Algorithm 5 Generates a Poisson random variable with parameter $r$

1: function GeneratePoisson($r$)
2: Set $p = \exp(-r)$, $s = p$, $n = 0$ and $u = \text{rand}()$
3: while $u > s$ do
4:   Update $n \leftarrow n + 1$, $p \leftarrow (pe^{-r})$ and $s \leftarrow s + p$
5: end while
6: return $n$
7: end function

Algorithm 6 Used to evaluate $D_{ki}$ given by (2.17)

1: function EvaluateCoupledDifference($x_1, x_2, T_f$)
2: Set $t = 0$
3: for $k = 1$ to $K$ do
4:   Set $T_{ki} = 0$ and $P_{ki} = -\log(\text{rand}())$ for $i = 1, 2, 3$
5: end for
6: while $x_1 \neq x_2$ AND $t < T_f$ do
7:   for $k = 1$ to $K$ do
8:     Set $A_{k1} = \lambda_0(x_1, \theta) \wedge \lambda_0(x_2, \theta)$, $A_{k2} = \lambda_0(x_1, \theta) - A_{k1}$ and $A_{k3} = \lambda_0(x_2, \theta) - A_{k1}$
9:     Set $\delta_{ki} = \left(\frac{P_{ki} - T_{ki}}{A_{ki}}\right)$ for $i = 1, 2, 3$
10: end for
11: Set $\Delta t = \min_{k, i}\{\delta_{ki}\}$ and $(k_m, i_m) = \arg \min_{k, i}\{\delta_{ki}\}$
12: Update $t \leftarrow t + \Delta t$
13: if $t < T_f$ then
14:   if $i_m = 1$ OR $i_m = 2$ then
15:     Update $x_1 \leftarrow x_1 + \zeta_{k_m}$
16:   end if
17:   if $i_m = 1$ OR $i_m = 3$ then
18:     Update $x_2 \leftarrow x_2 + \zeta_{k_m}$
19:   end if
20: for $k = 1$ to $K$ do
21:   Update $T_{ki} \leftarrow T_{ki} + A_{ki}\Delta t$ for $i = 1, 2, 3$
22: end for
23: Update $P_{k_m, i_m} \leftarrow P_{k_m, i_m} - \log(\text{rand}())$
24: end if
25: end while
26: return $f(x_1) - f(x_2)$
27: end function
4 Numerical Examples

In this section, we present many examples to compare the performance of PPA with the other methods for sensitivity estimation. Among these other methods, we consider the (unbiased) Girsanov method and the two best-performing finite-difference schemes, CFD and CRP. We can compare the performance of different methods by measuring the time they need to produce a *statistically accurate estimate* of the true sensitivity value \( S_\theta(f, T) \) given by (1.1). Such an estimate must be close to \( S_\theta(f, T) \) and it must have a small confidence interval. We now discuss how the time required to produce a statistically accurate estimate can be measured for both biased and unbiased methods.

Throughout this section, we represent the sensitivity estimate provided by a method as \( s \pm l \), which means that the 95% confidence interval is \([s - l, s + l]\), where the half-length \( l \) is given by (2.7). Suppose that the true value of \( S_\theta(f, T) \) is \( s_0 \) and a method estimates it as \( s \pm l \). We define the *estimation error* as

\[
\epsilon = \min_{x \in [s - l, s + l]} |x - s_0|, \tag{4.29}
\]

which is essentially the distance between the true sensitivity value \( s_0 \) and the 95% confidence interval \([s - l, s + l]\) produced by the estimation method. Notice that if \( s_0 \) is contained in \([s - l, s + l]\) then the estimation error \( \epsilon \) is 0. Since the unbiased schemes (Girsanov and PPA) estimate \( S_\theta(f, T) \) directly, we can expect \( \epsilon \) to be 0 as long as a sufficiently large sample is used for estimation. On the other hand, the finite-difference schemes (CFD and CRP) estimate \( S_\theta(h(f, T)) \) (see (1.2)) instead of the true value \( S_\theta(f, T) \) and hence \( \epsilon \) can be positive if the finite-difference is a poor approximation of the derivative. Observe that the one-point sensitivity estimate is \( s \) and so the estimation *bias* is simply \(|s - s_0|\). However this quantity is generally never 0 (even for unbiased schemes) and it can vary considerably with each run of the estimation procedure. Since the definition of the estimation error \( \epsilon \) involves the whole confidence interval \([s - l, s + l]\), it captures the estimation bias in a conservative and a statistically robust way. This is because \( \epsilon = 0 \) for \( s \) close to \( s_0 \), and for large sample sizes, different runs of the estimation procedure yield similar values of \( \epsilon \).

In this paper, we always estimate the sensitivity value \( S_\theta(f, t) \) using the minimum sample size \( (N) \) that is needed to produce an estimate of the form \( s \pm l \) for \( l \leq 0.05|s| \). In other words, we want the half-length of the 95% confidence interval to fall below 5% of the magnitude of the estimated sensitivity value \( s \). This way we ensure that the statistical precision is high or low depending on whether the sensitivity value is small or large. From now on, we call such an estimate of the sensitivity value as a *5%-estimate*.

We compare the efficiency of different methods by measuring the CPU time\(^3\) that is needed to generate a 5%-estimate with zero estimation error \( \epsilon \). For unbiased schemes, any 5%-estimate generally requires enough samples so that \( \epsilon = 0 \). However for finite-difference schemes, the estimation error \( \epsilon \) can be positive if \( h \) is not small enough. Recall from Section 2.1 that the variance of a finite-difference estimator scales like \( 1/h \), implying that if we take \( h \) to be too small then the method will become computationally infeasible. Since it is difficult to determine the optimum value of \( h \), we adopt the following strategy to gauge the efficiency of a finite-difference scheme. We start with \( h = 0.1 \) and generate a 5%-estimate along with the estimation error \( \epsilon \). If \( \epsilon = 0 \) then we stop here. Otherwise we decrease \( h \) by a factor of 10, to \( h = 0.01 \), and again obtain a 5%-estimate along with its \( \epsilon \). As before, we either stop if \( \epsilon = 0 \), or otherwise we repeat the process with \( h = 0.001 \). Continuing in this fashion, we will eventually find a \( h \) small enough so that a 5%-estimate has \( \epsilon = 0 \). For performance comparison, we use the CPU time corresponding to the highest value of \( h \) in the sequence 0.1, 0.01, 0.001, \ldots, for which the estimation error \( \epsilon \) is zero.

The computation of the estimation error \( \epsilon \) (see (4.29)) assumes that we know the exact sensitivity value \( S_\theta(f, T) = s_0 \). In some of our examples, \( S_\theta(f, T) \) can be analytically evaluated and hence the computation of \( \epsilon \) is quite straightforward. In other examples, where \( S_\theta(f, T) \) cannot be explicitly computed, we use PPA to produce an estimate \( \hat{s}_0 \pm l_0 \) with \( l_0 \leq 0.005|s_0| \), and then use \( \hat{s}_0 \) as a proxy for \( s_0 \) in evaluating \( \epsilon \). The rationale behind this is that since PPA is unbiased and \( l_0 \) is very small, \( \hat{s}_0 \) must be close to \( S_\theta(f, T) = s_0 \). Note that for most examples of practical interest \( S_\theta(f, T) \) is unknown and if we do not have the luxury of using an unbiased method, then it is difficult to measure the estimation error \( \epsilon \) incurred by a finite-difference scheme. Most practitioners who use finite-difference schemes, assume that \( \epsilon \) is small if \( h \) is small. However as our examples illustrate, \( \epsilon \) can be significant even for a \( h \) that appears small, potentially damaging the

---

\(^3\)All the computations in this paper were performed using C++ programs on an Apple machine with a 2.2 GHz Intel i7 processor.
accuracy of the sensitivity analysis. Therefore if a highly accurate estimate of \( S_\theta(f, T) \) is required for an application, then an unbiased method should be preferred over finite-difference schemes.

We now start discussing the examples. Recall that our method PPA depends on two parameters \( N_0 \) and \( M_0 \) whose choice is not very important (see Section 2.3). In all the examples we set \( N_0 = 100 \) and \( M_0 = 10 \). We mentioned before that the estimation error \( \epsilon \) is generally 0 for unbiased schemes, if a sufficiently large sample is used for estimation. This is always true for all our examples and hence we do not report \( \epsilon \) for unbiased schemes. In all the examples, the propensity functions \( \lambda_k \) are in the form of mass-action kinetics unless stated otherwise.

**Example 4.1 (Single-species birth-death model)** Our first example is a simple birth-death model in which a single species \( S \) is created and destroyed according to the following two reactions:

\[
\emptyset \xrightarrow{\theta_1} S \xrightarrow{\theta_2} \emptyset.
\]

Let \( \theta_1 = \theta_2 = 0.1 \) and assume that the sensitive parameter is \( \theta = \theta_2 \). Let \( (X(t))_{t \geq 0} \) be the Markov process representing the reaction dynamics. Hence the population of \( S \) at time \( t \) is given by \( X(t) \in N_0 \). Assume that \( X(0) = 0 \). For \( f(x) = x \) we wish to estimate

\[
S_\theta(f, T) = \frac{\partial}{\partial \theta} \mathbb{E}(f(X(T))) = \frac{\partial}{\partial \theta} \mathbb{E}(X(T)).
\]

for \( T = 20 \) and 100. Since the propensity functions of this network are affine, we can compute \( S_\theta(f, T) \) exactly. These exact values are given in Table 1. Next we obtain 5% estimates of the sensitivity value using unbiased schemes (Girsanov and PPA) and report the results in Table 2. Here \( N \) denotes the number of samples that were required and the sensitivity estimate is presented in the form of a 95% confidence interval \( s \pm l = [s - l, s + l] \). By comparing the CPU times, one can see that for this simple network, PPA is only about 1.5 times faster than the Girsanov method, on average. We shall soon see that as the networks get more complicated PPA can be several times faster than the Girsanov method.

| \( T \) | \( S_\theta(f, T) \) |
|-------|------------------|
| 20    | -5.9399          |
| 100   | -9.995           |

**Example 4.2 (Gene Expression Network)** Our second example considers the model for gene transcription given in [22]. It has three species: Gene (\( G \)), mRNA (\( M \)) and protein (\( P \)), and there are four reactions given by

\[
G \xrightarrow{\theta_1} G + M, \quad M \xrightarrow{\theta_2} M + P, \quad M \xrightarrow{\theta_3} \emptyset \quad \text{and} \quad P \xrightarrow{\theta_4} \emptyset.
\]

We now estimate \( S_\theta(f, T) \) using finite-difference schemes (CFD and CRP) with various values of \( h \). The results are in Table 3. Notice that as \( h \) gets smaller, the estimation error \( \epsilon \) reduces but the required CPU time rises. For \( T = 20 \), \( \epsilon = 0 \) was achieved for both CFD and CRP with \( h = 0.01 \). However for \( T = 100 \), CFD and CRP needed \( h = 0.001 \) for \( \epsilon \) to be zero. For performance comparison we only take those CPU times into account for which \( \epsilon = 0 \). The results indicate that on average, PPA is 7 times faster than CFD and 37 times faster than CRP.

This simple example shows that for finite-difference schemes, the estimation error \( \epsilon \) (and hence the bias) can be significant even if \( h \) seems small. Moreover our proposed method PPA can be faster than the finite-difference schemes if we pick a \( h \) small enough to ensure that \( \epsilon = 0 \).
The rate of translation of a gene into mRNA is \( \theta_1 \) while the rate of transcription of mRNA into protein is \( \theta_2 \). The degradation of mRNA and protein molecules occurs at rates \( \theta_3 \) and \( \theta_4 \) respectively. Typically \( \theta_3 \gg \theta_4 \) implying that a protein molecule lives much longer than a mRNA molecule. In the accordance with the values given in [22] for lacA gene in bacterium E.Coli, we set \( \theta_1 = 0.6 \text{ min}^{-1} \), \( \theta_2 = 1.7329 \text{ min}^{-1} \) and \( \theta_3 = 0.3466 \text{ min}^{-1} \). Our sensitive parameter is \( \theta = \theta_4 \).

Let \( (X(t))_{t \geq 0} \) be the \( \mathbb{N}_0^2 \)-valued Markov process representing the reaction dynamics. For any time \( t \), \( X(t) = (X_1(t), X_2(t)) \), where \( X_1(t) \) and \( X_2(t) \) are the number of mRNA and protein molecules respectively. We assume that \( (X_1(0), X_2(0)) = (0, 0) \) and define \( f : \mathbb{N}_0^2 \rightarrow \mathbb{R} \) by \( f(x_1, x_2) = x_2 \). We would like to estimate

\[
S_\theta(f, T) = \frac{\partial}{\partial \theta} \mathbb{E}(f(X(T))) = \frac{\partial}{\partial \theta} \mathbb{E}(X_2(T)),
\]

which measures the sensitivity of the mean of the protein population at time \( T \) with respect to the protein degradation rate.

For sensitivity estimation, we consider two values of \( T \) : 20 min and 100 min, and three values of \( \theta \): 0.0693 \text{ min}^{-1}, 0.0023 \text{ min}^{-1} and 0. These values of \( \theta \) correspond to the protein half-life of 10 min, 5 hr and \( \infty \). Like Example 4.1, this network also has affine propensity functions and hence we can compute \( S_\theta(f, T) \) exactly. These exact values are presented in Table 4. The results obtained by estimating the sensitivity

| \( T \) | \( h \) | Method | Sensitivity Estimate | \( N \) | CPU time (s) | Error (\( \epsilon \)) |
|---|---|---|---|---|---|---|
| 20 | 0.1 | CFD | \(-3.8397 \pm 0.1919\) | 2843 | 0.0184 | 1.9084 |
| | | CRP | \(-3.842 \pm 0.1920\) | 4239 | 0.1612 | 1.9059 |
| | 0.01 | CFD | \(-5.7114 \pm 0.2855\) | 25387 | 0.115 | 0 |
| | | CRP | \(-5.9209 \pm 0.296\) | 26228 | 0.8909 | 0 |
| 100 | 0.1 | CFD | \(-4.908 \pm 0.2454\) | 2226 | 0.0209 | 4.8417 |
| | | CRP | \(-5.1843 \pm 0.2592\) | 3255 | 0.1312 | 4.5515 |
| | 0.01 | CFD | \(-9.3231 \pm 0.4661\) | 14951 | 0.1245 | 0.2057 |
| | | CRP | \(-8.8918 \pm 0.4446\) | 17622 | 0.6902 | 0.6586 |
| 0.001 | CFD | \(-10.0894 \pm 0.5043\) | 150851 | 1.2404 | 0 |
| | | CRP | \(-9.7323 \pm 0.4866\) | 158441 | 5.9908 | 0 |

The rate of translation of a gene into mRNA is \( \theta_1 \) while the rate of transcription of mRNA into protein is \( \theta_2 \). The degradation of mRNA and protein molecules occurs at rates \( \theta_3 \) and \( \theta_4 \) respectively. Typically \( \theta_3 \gg \theta_4 \) implying that a protein molecule lives much longer than a mRNA molecule. In the accordance with the values given in [22] for lacA gene in bacterium E.Coli, we set \( \theta_1 = 0.6 \text{ min}^{-1} \), \( \theta_2 = 1.7329 \text{ min}^{-1} \) and \( \theta_3 = 0.3466 \text{ min}^{-1} \). Our sensitive parameter is \( \theta = \theta_4 \).

Let \( (X(t))_{t \geq 0} \) be the \( \mathbb{N}_0^2 \)-valued Markov process representing the reaction dynamics. For any time \( t \), \( X(t) = (X_1(t), X_2(t)) \), where \( X_1(t) \) and \( X_2(t) \) are the number of mRNA and protein molecules respectively. We assume that \( (X_1(0), X_2(0)) = (0, 0) \) and define \( f : \mathbb{N}_0^2 \rightarrow \mathbb{R} \) by \( f(x_1, x_2) = x_2 \). We would like to estimate

\[
S_\theta(f, T) = \frac{\partial}{\partial \theta} \mathbb{E}(f(X(T))) = \frac{\partial}{\partial \theta} \mathbb{E}(X_2(T)),
\]

which measures the sensitivity of the mean of the protein population at time \( T \) with respect to the protein degradation rate.

For sensitivity estimation, we consider two values of \( T \) : 20 min and 100 min, and three values of \( \theta \): 0.0693 \text{ min}^{-1}, 0.0023 \text{ min}^{-1} and 0. These values of \( \theta \) correspond to the protein half-life of 10 min, 5 hr and \( \infty \). Like Example 4.1, this network also has affine propensity functions and hence we can compute \( S_\theta(f, T) \) exactly. These exact values are presented in Table 4. The results obtained by estimating the sensitivity

| \( \theta \) | \( T \) | \( S_\theta(f, T) \) |
|---|---|---|
| 0.0693 | 20 | -207.544 |
| | 100 | -618.776 |
| 0.0023 | 20 | -439.001 |
| | 100 | -12213.9 |
| 0 | 20 | -451.812 |
| | 100 | -14158.6 |

values with unbiased schemes are shown in Table 5. For \( \theta = 0 \), the Girsanov method cannot be used (see Section 2.2) and therefore the results are only provided for PPA. From Table 5 it is immediate that PPA can be far more efficient than the Girsanov method. On average PPA is 71 times faster for \( \theta = 0.0693 \text{ min}^{-1} \) and 2781 times faster for \( \theta = 0.0023 \text{ min}^{-1} \). Unlike PPA, the performance of the Girsanov method deteriorates drastically as \( \theta \) gets smaller. This observation is consistent with the results in [14].

We now estimate \( S_\theta(f, T) \) using finite-difference schemes. With \( h = 0.1 \), for all the values of \( \theta \) and \( T \) both CFD and CRP produced an estimate with a positive estimation error \( \epsilon \) (data not shown). When we reduce \( h \) to 0.01, the results we obtain are given in Table 6. As with \( h = 0.1 \), all the estimates carry a positive \( \epsilon \). Hence we decrease \( h \) to 0.001 and re-estimate the sensitivity values. The results are presented in Table 7. Now \( \epsilon = 0 \) in all the cases and hence we can use these results for performance comparison. On average PPA is 2 times faster than CRP but 1.5 times slower than CFD. Even though PPA is slightly slower than CFD,
its unbiasedness guarantees that the estimation error $\epsilon$ is 0, and one does not require additional checks to verify its accuracy.

Table 5: Gene Expression network : Unbiased schemes

| $\theta$ | T | Method | Sensitivity Estimate | N | CPU time (s) |
|----------|---|--------|----------------------|---|--------------|
| 0.0693   | 20| Girsanov | $-208.032 \pm 10.4002$ | 224176 | 3.7808 |
|          |   | PPA     | $-205.082 \pm 10.2471$ | 482  | 0.0804 |
|          | 100| Girsanov | $-619.598 \pm 30.9777$ | 457481 | 47.1516 |
|          |   | PPA     | $-625.577 \pm 31.2622$ | 1085 | 0.6325 |

| 0.0023   | 20| Girsanov | $-437.824 \pm 21.891$ | 6097447 | 101.034 |
|          |   | PPA     | $-444.088 \pm 22.2001$ | 534  | 0.0714 |
|          | 100| Girsanov | $-12423.1 \pm 621.137$ | 4287726 | 501.094 |
|          |   | PPA     | $-12319.9 \pm 613.782$ | 197  | 0.1451 |

| 0        | 20| PPA     | $-437.588 \pm 21.8528$ | 533  | 0.0675 |
|          | 100| PPA     | $-14033.5 \pm 699.9$ | 235  | 0.151 |

Example 4.3 (Circadian Clock Network) We now consider the network of a circadian clock introduced and studied by Vilar et. al. [23]. It is a large network with 9 species $S_1, \ldots, S_9$ and 16 reactions. These reactions along with the rate constants are given in Table 8. Let $(X(t))_{t \geq 0}$ be the $\mathbb{N}_0^9$-valued Markov process corresponding to the reaction dynamics with initial state $X(0) = (1, 0, 0, 1, 0, 0, 0, 0, 0)$. For $T = 5$ and $f(x) = x_4$ we wish to estimate

$$S_\theta(f, T) = \frac{\partial}{\partial \theta} \mathbb{E}(f(X(T))) = \frac{\partial}{\partial \theta} \mathbb{E}(X_4(T)),$$

for $\theta = \theta_i$ and $i = 5, 6, 8, 12$ and 14.

Due to the presence of many bimolecular interactions, exact values of $S_\theta(f, T)$ are difficult to compute analytically. In order to measure the estimation error $\epsilon$ we need a proxy for $S_\theta(f, T)$. For this we use PPA to produce sensitivity 0.5%-estimates of the form $\hat{s}_0 \pm l_0$ with $l_0 \leq 0.005 |\hat{s}_0|$, and then use $\hat{s}_0$ for evaluating $\epsilon$. These values of $\hat{s}_0$ are presented in Table 9. The results we obtain on estimating the sensitivity values with unbiased schemes are shown in Table 10. As in the previous example, these results indicate that PPA has much better performance than the Girsanov method. On average PPA is around 1760 times faster than the Girsanov method.

We now estimate $S_\theta(f, T)$ using finite-difference schemes with $h = 0.1$. The results are presented in Table 11. For three of the five values of $\theta$, the estimation error $\epsilon$ is 0. For the other two values ($\theta = \theta_5$ and $\theta_6$), we estimate $S_\theta(f, T)$ using finite-difference schemes with $h = 0.01$ and display the results in Table 12. Now $\epsilon = 0$ for these two values as well. For performance comparison, we consider the CPU times for $\theta = \theta_5, \theta_6$.
Table 7: Gene Expression network : finite-difference schemes with $h = 0.001$

| $\theta$ | | Method | Sensitivity Estimate | $N$ | CPU time (s) | Error ($\epsilon$) |
|---------|---------|---------|----------------------|------|--------------|-------------------|
| 0.0693  | 20      | CFD     | $-201.543 \pm 10.0744$ | 6092 | 0.2384       | 0                 |
|         | 100     | CRP     | $-207.91 \pm 10.3918$  | 7382 | 0.7723       | 0                 |
|         |         | CRP     | $-622.523 \pm 31.1192$  | 958  | 0.2389       | 0                 |
|         |         | CFD     | $-620.455 \pm 31.0144$  | 2502 | 0.6615       | 0                 |
| 0.0023  | 20      | CFD     | $-439.978 \pm 21.9898$  | 3606 | 0.1138       | 0                 |
|         | 100     | CRP     | $-435.451 \pm 21.767$   | 3965 | 0.4024       | 0                 |
|         |         | CFD     | $-11171.1 \pm 585.652$  | 204  | 0.0361       | 0                 |
|         |         | CRP     | $-11177.9 \pm 586.951$  | 208  | 0.0421       | 0                 |
| 0       | 20      | CFD     | $-443.079 \pm 22.1501$  | 3741 | 0.1152       | 0                 |
|         | 100     | CRP     | $-441.116 \pm 22.0505$  | 3871 | 0.3243       | 0                 |
|         |         | CFD     | $-13744.9 \pm 685.645$  | 195  | 0.0339       | 0                 |
|         |         | CRP     | $-13767.3 \pm 685.809$  | 158  | 0.0606       | 0                 |

Table 8: Circadian Clock network : List of reactions

| No. | Reaction | Rate Constant | No. | Reaction | Rate Constant |
|-----|----------|---------------|-----|----------|---------------|
| 1   | $S_6 + S_2 \rightarrow S_7$ | $\theta_1 = 1$ | 9   | $S_2 \rightarrow \emptyset$ | $\theta_9 = 100$ |
| 2   | $S_7 \rightarrow S_6 + S_2$ | $\theta_2 = 50$ | 10  | $S_0 \rightarrow S_0 + S_3$ | $\theta_{10} = 0.01$ |
| 3   | $S_6 + S_2 \rightarrow S_0$ | $\theta_3 = 50$ | 11  | $S_8 \rightarrow S_8 + S_3$ | $\theta_{11} = 50$ |
| 4   | $S_0 \rightarrow S_8 + S_2$ | $\theta_4 = 500$ | 12  | $S_3 \rightarrow \emptyset$ | $\theta_{12} = 0.5$ |
| 5   | $S_7 \rightarrow S_7 + S_1$ | $\theta_5 = 10$ | 13  | $S_3 \rightarrow S_3 + S_4$ | $\theta_{13} = 5$ |
| 6   | $S_6 \rightarrow S_6 + S_1$ | $\theta_6 = 50$ | 14  | $S_4 \rightarrow \emptyset$ | $\theta_{14} = 0.2$ |
| 7   | $S_1 \rightarrow \emptyset$ | $\theta_7 = 1$ | 15  | $S_2 + S_4 \rightarrow S_5$ | $\theta_{15} = 20$ |
| 8   | $S_1 \rightarrow S_1 + S_2$ | $\theta_8 = 1$ | 16  | $S_5 \rightarrow S_4$ | $\theta_{16} = 1$ |

and $\theta_{14}$ from Table 11, and $\theta = \theta_8$ and $\theta_{12}$ from Table 12. Overall, PPA is 23 times more efficient than CFD and 50 times more efficient that CRP.

**Example 4.4 (Genetic toggle switch)** In our last example we look at a simple network with nonlinear propensity functions. Consider the network of a genetic toggle switch proposed by Gardner et. al. [9]. This network has two species $U$ and $V$ that interact through the following four reactions

$$
\emptyset \xrightarrow{\lambda_1} U, \quad U \xrightarrow{\lambda_2} \emptyset, \quad \emptyset \xrightarrow{\lambda_3} V \quad \text{and} \quad V \xrightarrow{\lambda_4} \emptyset,
$$

where the propensity functions $\lambda_i$-s are given by

$$
\lambda_1(x_1, x_2) = \frac{\alpha_1}{1 + x_2^2}, \quad \lambda_2(x_1, x_2) = x_1, \quad \lambda_3(x_1, x_2) = \frac{\alpha_2}{1 + x_1} \quad \text{and} \quad \lambda_4(x_1, x_2) = x_2.
$$

In the above expressions, $x_1$ and $x_2$ denote the number of molecules of $U$ and $V$ respectively. We set $\alpha_1 = 50, \alpha_2 = 16, \beta = 2.5$ and $\gamma = 1$. Let $(X(t))_{t \geq 0}$ be the $\mathbb{N}_0^2$-valued Markov process representing the reaction dynamics with initial state $(X_1(0), X_2(0)) = (0, 0)$. For $T = 10$ and $f(x) = x_1$, our goal is to estimate

$$
S_\theta(f, T) = \frac{\partial}{\partial \theta} \mathbb{E}(f(X(T))) = \frac{\partial}{\partial \theta} \mathbb{E}(X_1(T)),
$$

for $\theta = \alpha_1, \alpha_2, \beta$ and $\gamma$. In other words, we would like to measure the sensitivity of the mean of the number of $U$ molecules at time $T = 10$, with respect to all the model parameters.

Table 9: Circadian clock network : Approximate values of $S_\theta(f, T)$

| $\theta$ | $\theta_8 = 1$ | $\theta_8 = 0.5$ | $\theta_8 = 0.2$ |
|----------|----------------|-----------------|-----------------|
| $S_\theta(f, T)$ | $-240.368$ | $47.0746$ | $-127.629$ | $1469.81$ | $0.1424$ |

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Table 10: Circadian clock network: Unbiased schemes

| θ   | Method | Sensitivity Estimate | N     | CPU time (s) |
|-----|--------|----------------------|-------|--------------|
| 5   | Girsanov | −243.012 ± 12.1506 | 679988 | 5337.59      |
|     | PPA     | −245.176 ± 12.251   | 1110  | 135.562      |
| 6   | Girsanov | 47.4759 ± 2.37376   | 3720521 | 35309.9     |
|     | PPA     | 47.6519 ± 2.38098   | 1474  | 157.202      |
| 8   | Girsanov | −131.408 ± 6.57038  | 4514357 | 755441      |
|     | PPA     | −128.405 ± 6.4184   | 8707  | 230.939      |
| 12  | Girsanov | 1414.23 ± 70.7093   | 461710 | 6208.21     |
|     | PPA     | 1487.72 ± 74.2374   | 315   | 68.8725      |
| 14  | Girsanov | 0.0212 ± 0.0077     | 3762440 | 843006      |
|     | PPA     | 0.1487 ± 0.0074     | 403   | 59.5083      |

Table 11: Circadian clock network: finite-difference schemes with h = 0.1

| θ   | Method | Sensitivity Estimate | N     | CPU time (s) | Error (ε) |
|-----|--------|----------------------|-------|--------------|-----------|
| 5   | CFD    | −242.463 ± 12.0954  | 271   | 9.49         | 0         |
|     | CRP    | −236.318 ± 11.8096  | 572   | 12.1228      | 0         |
| 6   | CFD    | 46.8224 ± 2.3409    | 855   | 29.681       | 0         |
|     | CRP    | 47.8721 ± 2.393     | 2955  | 64.8373      | 0         |
| 8   | CFD    | −112.413 ± 5.6172   | 2183  | 79.8562      | 9.5988    |
|     | CRP    | −118.141 ± 5.9063   | 709   | 15.1828      | 3.5818    |
| 12  | CFD    | 1304.87 ± 65.1674   | 75    | 2.6899       | 99.7741   |
|     | CRP    | 1273.54 ± 63.3941   | 47    | 1.0043       | 132.874   |
| 14  | CFD    | 0.1404 ± 0.0007     | 300967 | 14184.5      | 0         |
|     | CRP    | 0.1408 ± 0.0007     | 458117 | 32766.1      | 0         |

Table 12: Circadian clock network: finite-difference schemes with h = 0.01

| θ   | Method | Sensitivity Estimate | N     | CPU time (s) | Error (ε) |
|-----|--------|----------------------|-------|--------------|-----------|
| 8   | CFD    | −127.209 ± 6.3597   | 19680 | 981.825      | 0         |
|     | CRP    | −128.559 ± 6.4272   | 6638  | 183.272      | 0         |
| 12  | CFD    | 1493.99 ± 74.6416   | 714   | 31.8758      | 0         |
|     | CRP    | 1466.35 ± 73.2438   | 418   | 8.912        | 0         |
Since the form of the propensity functions $\lambda_1$ and $\lambda_3$ is nonlinear, it is hard to compute $S_{\theta}(f, T)$ exactly. As in the previous example, we obtain a close approximation of $S_{\theta}(f, T)$ by computing a 0.5%-estimate using PPA. These approximate values are presented in Table 13 for various values of $\theta$. When we estimate the sensitivity values using unbiased schemes, then we obtain the results in Table 14. On comparing the CPU times we find that overall PPA is nearly 7 times more efficient than the Girsanov method.

| $\theta$ | Method | Sensitivity Estimate | $N$ | CPU time (s) |
|----------|--------|----------------------|-----|--------------|
| $\alpha_1 = 50$ | Girsanov | $1.1878 \pm 0.0594$ | 244536 | 99.3652 |
| Girsanov | $1.2038 \pm 0.0602$ | 13296 | 11.8902 |
| PPA | $1.1919$ | $-2.107$ | $-5.9571$ | $54.7495$ |
| $\alpha_2 = 16$ | Girsanov | $-2.0936 \pm 0.1047$ | 9792 | 1.719 |
| Girsanov | $-2.078 \pm 0.1039$ | 5772 | 3.5082 |
| PPA | $-2.1092 \pm 0.1054$ | $239384$ | $132.736$ |
| $\beta = 2.5$ | Girsanov | $-5.7873 \pm 0.2893$ | $163088$ | $55.2828$ |
| PPA | $-6.0166 \pm 0.3008$ | $9662$ | $6.4339$ |
| $\gamma = 1$ | Girsanov | $53.1406 \pm 2.6569$ | $31813$ | $6.1669$ |
| CRP | $54.3517 \pm 2.7157$ | $1505$ | $1.8537$ |

We now estimate $S_{\theta}(f, T)$ using finite-difference schemes with $h = 0.1$. The results in Table 15 show that the estimation error $\epsilon$ is 0 for all the parameters except $\gamma$. Hence we again estimate $S_{\theta}(f, T)$ for $\theta = \gamma$ using finite-difference schemes with $h = 0.01$ and report the results in Table 16. Now $\epsilon = 0$ for parameter $\gamma$ as well. From the CPU times given in Tables 15 and 16 one can check that PPA is 11.5 times faster than CFD and 40 times faster than CRP.

| $\theta$ | Method | Sensitivity Estimate | $N$ | CPU time (s) | Error ($\epsilon$) |
|----------|--------|----------------------|-----|--------------|--------------------|
| $\alpha_1 = 50$ | CFD | $1.1705 \pm 0.0585$ | $202550$ | $64.8713$ | 0 |
| CRP | $1.1744 \pm 0.0587$ | $680082$ | $470.17$ | 0 |
| $\alpha_2 = 16$ | CFD | $-2.1092 \pm 0.1054$ | $239384$ | $132.736$ | 0 |
| CRP | $-2.1656 \pm 0.1083$ | $550949$ | $349.655$ | 0 |
| $\beta = 2.5$ | CFD | $-5.7835 \pm 0.2891$ | $93255$ | $52.4236$ | 0 |
| CRP | $-5.8088 \pm 0.2904$ | $136371$ | $73.4986$ | 0 |
| $\gamma = 1$ | CFD | $46.6615 \pm 2.3235$ | $7781$ | $2.971$ | $5.7555$ |
| CRP | $46.168 \pm 2.3084$ | $14879$ | $5.9668$ | $6.2731$ |

The examples presented in this section illustrate the following:

- In producing an estimate with a specified statistical accuracy, PPA can be several times faster than the Girsanov method.

- If we pick a $h$ small enough to ensure that the estimation error $\epsilon$ is 0, then PPA can even be more efficient than the finite-difference schemes (CFD and CRP).

5 Conclusions and Future Work

The aim of this paper is to provide a new unbiased method for estimating parameter sensitivity of stochastic reaction networks. Using a result from our recent paper [14], we construct a random variable whose expectation is the required sensitivity value. We then present a simple procedure, called the Poisson Path Algorithm...
(PPA), to compute the realizations of this random variable. This gives us a way to generate samples for estimating the parameter sensitivity. Our method can be viewed as an improved version of the Auxiliary Path Algorithm (APA), that we presented in [14]. Unlike APA, the proposed method is easy to implement, has low memory requirements and it works well for large networks and large observation times.

Through examples we compare the performance of PPA with other methods for sensitivity estimation, both biased and unbiased. Our results indicate that PPA easily outperforms the unbiased Girsanov method. Moreover in many cases it can be significantly faster that the best-performing finite-difference schemes (CRP and CFD) in producing a statistically accurate estimate. This makes PPA an appealing method for sensitivity estimation because it is computationally efficient and one does not have to tolerate a bias of an unknown size, that is introduced by finite-difference approximations.

In our method we simulate the paths of the underlying Markov process using Gillespie’s Stochastic Simulation Algorithm (SSA) [11]. However SSA is very meticulous in the sense that it simulates the occurrence of each and every reaction in the dynamics. This can be very cumbersome for large networks with many reactions. To resolve this problem, a class of $\tau$-leaping methods have been developed (see [12, 4]). These methods are approximate in nature but they significantly reduce the computational effort that is required to simulate the reaction dynamics. In future we would like to develop a version of PPA that uses a $\tau$-leaping method instead of SSA and still produces an accurate estimate for the sensitivity values. Such a method would greatly simplify the sensitivity analysis of large networks.

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