

Low variability estimators for sensitivity analysis of stochastic biochemical reaction systems

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Short Abstract — We present a method for computing the parametric sensitivity of stochastic biochemical reaction systems using the random time change (RTC) representation of a discrete Markov process. The proposed method estimates the sensitivity via a finite difference approximation using coupled rather than independent sample paths, which reduces the variance of the estimate significantly due to the positive correlation of the paths. Applying the method to a simple monomolecular example and comparing results with alternative methods, we find improvements in relative error and reduced variance for a given sample size.

Keywords — sensitivity analysis, random time change.

I. INTRODUCTION

HERE we consider the problem of computing the parametric sensitivities of a discrete stochastic chemical reaction system via a finite difference approximation. Using the *random time change* (RTC) representation for Markov processes [1,2], we present a new method for sensitivity estimation that offers improved accuracy and faster convergence compared to independent Monte Carlo methods. This method is distinct from other approaches used to address this problem (see, e.g. [3,4]).

II. FINITE DIFFERENCE ESTIMATES OF SENSITIVITY

One way to numerically compute the parametric sensitivity of a discrete stochastic system is via a finite difference estimator. For simplicity, we only consider a forward difference approximation here. The estimated values for the nominal process and the process with one perturbed parameter are each estimated from the mean of samples obtained independently using an exact stochastic simulation algorithm (SSA), such as the Gillespie algorithm [5].

The accuracy of the estimator can be assessed through its variance. When the estimator uses independent samples of random variables (a common practice), one can reduce the variance only by taking more samples. If instead the estimator uses positively correlated replicates, then the variance can be decreased for a fixed number of samples relative to the independent method. This concept is known as the method of common random numbers (CRN) [6]. It

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can be applied to the problem of sensitivity analysis by computing many coupled sample paths of the nominal and perturbed processes, sharing the same pair of uniform random numbers used in the SSA for each replicate. Hereafter we shall refer to this method as the coupled estimator, distinct from the independent method described previously.

III. RANDOM TIME CHANGE REPRESENTATION

An equivalent way to represent a stochastic chemical reaction system is by explicitly considering the *internal times* of each reaction, given by independent unit rate Poisson processes. This is the RTC representation, which is possible for general Markov processes and has recently been used to develop a modified next reaction SSA [1,2]. It allows the driving noise processes to be described independently of the state and the state- and parameter-dependent propensity functions. Thus, one can readily implement the CRN method in conjunction with the modified next reaction SSA from [2] to estimate the sensitivities by using identical m-tuples of exponential random numbers (here, the internal reaction times) in each replicate for both the nominal and the perturbed processes. We refer to this as the coupled RTC method.

IV. NUMERICAL RESULTS

A numerical experiment was performed to compute the sensitivity coefficients for the monomolecular birth-death process with respect to its kinetic parameters using the independent, coupled, and coupled RTC estimators. Both the coupled and coupled RTC methods achieved significantly lower relative error estimates compared to the independent method as the increment size decreased. Additionally, the coupled RTC estimates achieved lower relative error than the coupled estimates, especially at smaller increments.

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