Low variability estimators for sensitivity analysis of stochastic biochemical reaction systems

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***Short Abstract* — We present the common reaction path (CRP) method for computing the parametric sensitivity of stochastic biochemical reaction systems. The proposed method uses the random time change representation of a discrete Markov process to estimate the sensitivity via a finite difference approximation with 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 example biochemical networks and comparing results found by alternative methods, we find improvements in relative error and reduced variance for a given sample size.**

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* representation for Markov processes [1,2], we present a new method for sensitivity estimation, the *common reaction path* (CRP) method, 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 evolution of the process with parameter set c and of the process with perturbed $c+h$ 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 by its variance. When the estimator uses independent random numbers to generate the samples (a common practice which we refer to hereafter as IRN), one can reduce the variance only by taking more samples. If instead the estimator uses positively correlated replicates, then the variance can be decreased compared to IRN for a fixed number of samples. This concept is known as the method of common random numbers (CRN) [6]. It can be applied to the problem of sensitivity analysis by computing many coupled sample paths of the nominal and perturbed processes, sharing the same set of uniform random numbers used in the SSA for each replicate. Hereafter we shall refer to this method as the CRN method, distinct from the IRN described previously.

III. Random Time Change Representation

An equivalent way to represent a stochastic chemical reaction system is by the random time change representation. This explicitly considers the *internal times* of each reaction channel, given by independent unit rate Poisson processes. This 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 employ CRN in conjunction with a modified SSA algorithm similar to [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 simulation process as the common reaction path method (CRP).

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 IRN, CRN and CRP estimators. Both the CRN and CRP methods achieved significantly lower relative error estimates compared to the IRN method as the increment size decreased. Additionally, the CRP estimates achieved lower relative error than CRN estimates, especially at small h.

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