

Parametric Sensitivity Analysis for Models of Reaction Networks within Interacting Compartments

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Models of reaction networks within interacting compartments (RNIC) are a generalization of stochastic reaction networks. It is most natural to think of the interacting compartments as “cells” that can appear, degrade, split, and even merge, with each cell containing an evolving copy of the underlying stochastic reaction network. Such models have a number of parameters, including those associated with the internal chemical model and those associated with the compartment interactions, and it is natural to want efficient computational methods for the numerical estimation of sensitivities of model statistics with respect to these parameters. Motivated by the extensive work on computational methods for parametric sensitivity analysis in the context of stochastic reaction networks over the past few decades, we provide a number of methods in the basic RNIC setting. Provided methods include the (unbiased) Girsanov transformation method (also called the Likelihood Ratio method) and a number of coupling methods for the implementation of finite differences, each motivated by methods from previous work related to stochastic reaction networks. We provide several numerical examples comparing the various methods in the new setting. We find that the relative performance of each method is in line with its analog in the “standard” stochastic reaction network setting. We have made all of the Matlab code used to implement the various methods freely available for download.

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I. INTRODUCTION

The last few decades have seen a large amount of research focused on utilizing stochastic reaction networks to understand myriad processes, including gene regulatory networks, viral and bacterial infections, and more¹⁻⁹. The standard mathematical model for a stochastic reaction network treats the system as a continuous-time Markov chain on $\mathbb{Z}_{\geq 0}^d$, where d is the number of species of the system, with reactions determining the state transitions of the model. Such mathematical models are typically used under the assumption that the real-world system being studied resides within a “well-stirred” environment. See Refs. 10 and 11 for a general (mathematical) introduction to such models. These models are often simulated via the so-called “Gillespie algorithm” named after Dan Gillespie who wrote some of the seminal papers on these models in the mid-1970s^{12,13}.

The assumption that the system of interest resides within a well-stirred environment can be generalized in numerous ways, depending on the problem being studied. For example, in some situations it may be natural to track the position of individual molecules, either in a discretized space or a continuous space setting¹⁴⁻¹⁷. Another approach, and the one we take here, is to assume the existence of multiple interacting “compartments” (or cells) each of which contains an evolving copy of a given stochastic reaction network. This approach is useful in numerous modeling scenarios including the dynamics of membrane-bound organelles¹⁸, the study of clustering proteins¹⁹, and the dynamics of clonal cells during their development²⁰. In Ref. 21, a modeling framework was formalized for this type of system which can be briefly summarized in the following manner.

- There are a number of “compartments” (one can think of them as cells) that are interacting dynamically. Following the language of Ref. 21, the four types of interactions for the compartments are: (i) inflows (compartments spontaneously appear at some rate), (ii) outflows (compartments spontaneously disappear, or die), (iii) coagulation or the merger of two compartments, and (iv) fragmentation (a compartment divides into two compartments).
- Each compartment contains an evolving copy of a given stochastic reaction network. The stochastic reaction networks evolve independently between compartment events/interactions.

- When a compartment appears, the initial state of its contents is chosen from a given distribution on $\mathbb{Z}_{\geq 0}^d$. We will later denote this distribution by μ .
- When a compartment disappears, its contents disappear as well.
- When compartments merge, their contents combine.
- When a compartment fragments, the contents are randomly split between the two compartments.

A first comprehensive mathematical analysis of these models (with results related to such basic questions as transience, recurrence, explosiveness, stationary behavior, etc.) can be found in Ref. 22. We note that a different model, also considered in Ref. 21, allows for the rates associated with compartment events (such as mergers and fragmentations) to depend upon the contents of the different compartments. Such models are not considered within this paper. Extending the methods presented here to that modeling scenario is a reasonable avenue of future work, as pointed out in our Discussion Section V.

These RNIC models have many parameters: those associated with the reaction network (evolving within each compartment), the parameters associated with the evolving compartment model, the parameters of the initial distribution for when compartments appear, etc. When working with any mathematical model a critical question is: how sensitive is the model to perturbations in its parameters? As we are dealing with a stochastic process, the most natural way to pose this question is as follows: what are the derivatives of the relevant expectations of the model? Here the “relevant expectations” will depend upon the model being studied and the questions being posed, but could include expected numbers of certain species (summed over all the compartments, perhaps) at a given time, the probability of the model being in a certain region of state space at a given time, etc. The study of such derivatives is typically called *parametric sensitivity analysis* and plays a critical role in the computational study of stochastic models in all fields that utilize them^{23–29}.

In this paper, we provide a number of computational methods that estimate derivatives of expectations of RNIC models. In particular, we provide a Girsanov transformation method (also termed a likelihood transformation method), which is unbiased, and a number of finite difference methods. Finite difference methods require a perturbation parameter h , where smaller values of h reduce bias but increase variance (see Appendix A). We do not provide

any pathwise differentiation methods (also termed *Infinitesimal Perturbation Analysis*) as stochastic reaction networks (and, hence, RNIC models) nearly always have “interruptions,” ensuring these methods are not valid in this context^{30,31}. The finite difference methods provided here are each based off a different coupling strategy taken from the computational stochastic reaction network literature. These couplings are: Common Random Variables (CRV) (i.e., using the same seeds for the random number generator), the Common Reaction Path (CRP) method³², the local Common Reaction Path method (local-CRP)³³, and the Split Coupling method^{26,34}. We do not attempt to extend other methods from the stochastic reaction network literature, such as the Auxiliary Path Algorithm³⁵, the Poisson Path Algorithm³⁶, the hybrid pathwise approach³¹ or the Integral Path Algorithm³⁷ as they are beyond the scope of this article (which mostly focuses on finite difference methods). However, these can sometimes be low variance, unbiased alternatives to the Girsanov transformation method and extending them would be a reasonable project in the future, as we mention in our Discussion Section V.

We provide a number of numerical examples, with perturbations in both the chemical and compartment parameters. Our general conclusions follow similar conclusions from parametric sensitivity analysis for “standard” stochastic reaction networks. Specifically, because the Girsanov method is unbiased and easy to implement, it should be attempted first. However, if the Girsanov method provides variances that are too large for a particular computational budget, then a finite difference method should be implemented. In that case, the Split Coupling is a good method to choose when one parameter, or a small number of parameters, is being perturbed. However, if a large number of parameters are being perturbed, then the CRP methods could be the most efficient.

The remainder of the paper is arranged as follows. In Section II, we formally introduce the relevant mathematical models, including both the standard model of stochastic reaction networks and the RNIC model. In Section III, we provide various computational methods for the estimation of parametric sensitivities. In particular, we demonstrate how to implement the Girsanov transformation method and the Split Coupling in the RNIC context. In Section IV, we provide a number of computational examples. Finally, in Section V, we discuss our findings and suggest some avenues of future work. In the appendix Section A, and for the sake of completeness, we give a very brief introduction to Monte Carlo methods in the context of estimating parametric sensitivities with finite difference methods. In the appendix

Section B, we provide a number of algorithms that are utilized for the standard stochastic reaction network models (as introduced in Section II).

II. MATHEMATICAL MODELS

We first introduce the standard model for stochastic reaction networks in Section II A. Next, in Section II B, we introduce the RNIC model. We also provide in Algorithm 1 a pseudo-algorithm for generating a single trajectory of an RNIC model.

A. Stochastic reaction networks

We begin with the definition of a reaction network.

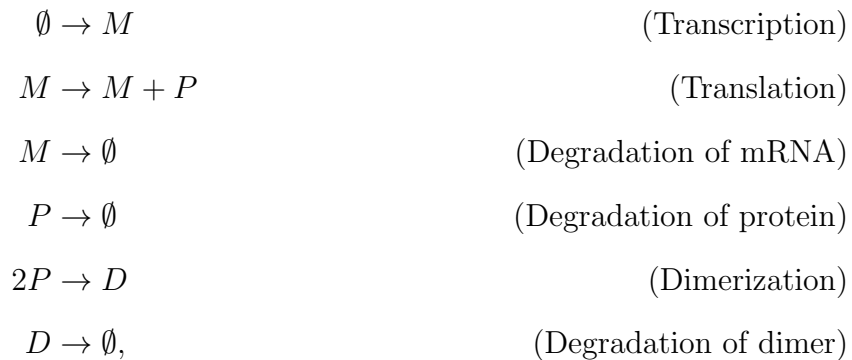
Definition 1. A *reaction network* is a triple of non-empty, finite sets, usually denoted $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$.

1. *Species*, \mathcal{S} : the components whose abundances we wish to model dynamically.
2. *Complexes*, \mathcal{C} : non-negative integer linear combinations of the species.
3. *Reactions*, \mathcal{R} : a binary relation on the complexes. The relation is often denoted “ \rightarrow ”.

For $y, y' \in \mathcal{C}$ with $y \rightarrow y' \in \mathcal{R}$, we call y and y' the *source* and *product* complexes of that reaction, respectively. We write \emptyset for the complex with all zero coefficients. \triangle

An example demonstrates the terminology.

Example 1. Consider a standard model of transcription and translation, with protein dimerization (see Example 2.4 in Ref. 11):



where M represents mRNA, P represents protein, and D represents dimer. We are assuming the cell has one gene, and so we suppress that species.

For this model, the set of species is $\mathcal{S} = \{M, P, D\}$, the set of complexes is $\mathcal{C} = \{\emptyset, M, P, M + P, 2P, D\}$, and the six reaction types are as above, $\mathcal{R} = \{\emptyset \rightarrow M, M \rightarrow M + P, M \rightarrow \emptyset, \dots\}$. \square

Returning to the general case, we fix notation and assume there are d species, which we label as $\{S_1, \dots, S_d\}$. We will denote the process by X , so that $X(t) \in \mathbb{Z}_{\geq 0}^d$ gives the state at time $t \geq 0$. Therefore, $X(t)$ is a vector giving the abundance of molecules of each species at the specified time. The state transitions for the model are then determined by the different reactions. For the k th reaction, we let $y_k \in \mathbb{Z}_{\geq 0}^d$ and $y'_k \in \mathbb{Z}_{\geq 0}^d$ be the vectors whose i th component gives the multiplicity of species i in the source and product complexes, respectively, and let $\lambda_k : \mathbb{Z}_{\geq 0}^d \rightarrow \mathbb{R}_{\geq 0}$ give the *transition intensity*, or rate, at which the reaction occurs. (Note that in the biological and chemical literature transition intensities are referred to as *propensities*^{12,13}.) If the k th reaction occurs at time t , then the old state, $X(t-)$, is updated by addition of the *reaction vector*

$$\zeta_k := y'_k - y_k$$

and the new state is given as $X(t) = X(t-) + \zeta_k$. Here, by $X(t-)$ we mean the left-sided limit $\lim_{s \rightarrow t-} X(s)$. For example, if a model consists of the three species $\{S_1, S_2, S_3\}$ and if the reaction type $S_1 + S_2 \rightarrow S_3$ takes place, then we would update with

$$y_k = \begin{bmatrix} 1 \\ 1 \\ 0 \end{bmatrix}, \quad y'_k = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}, \quad \text{and} \quad \zeta_k = \begin{bmatrix} -1 \\ -1 \\ 1 \end{bmatrix}.$$

Denoting the number of times the k th reaction occurs by time t as $R_k(t)$, simple book-keeping implies

$$X(t) = X(0) + \sum_k R_k(t) \zeta_k,$$

where the sum is over reactions. Note that each R_k is a counting process (starts at 0 and can only change by increases of size +1) with intensity $\lambda_k(X(t))$. Letting $\{Y_k\}$ be independent unit-rate Poisson processes, Kurtz's representation (which is useful for both analysis and computation) has $R_k(t) = Y_k(\int_0^t \lambda_k(X(s)) ds)$ ^{11,38}. Hence, the model satisfies the following

equation, which is often termed the *random time change representation* of Kurtz:

$$X(t) = X(0) + \sum_k Y_k \left(\int_0^t \lambda_k(X(s)) ds \right) \zeta_k, \quad (1)$$

where the sum is over the reaction types. We will denote a family of such models, parameterized by θ (which, in the case of stochastic mass-action kinetics—see below in (3)—is most likely a rate constant, κ_k , of the system), as

$$X^\theta(t) = X^\theta(0) + \sum_k Y_k \left(\int_0^t \lambda_k^\theta(X^\theta(s)) ds \right) \zeta_k. \quad (2)$$

The most common, though certainly not the only, choice of intensity function λ_k is that of stochastic *mass-action kinetics*. The stochastic form of the law of mass-action says that for some constant κ_k the rate of the k th reaction is

$$\lambda_k(x) = \kappa_k \prod_i \frac{x_i!}{(x_i - y_{k,i})!} \quad (3)$$

where $y_{k,i}$ is the i th component of the source complex y_k .³⁹ The rate constants are typically placed next to their reaction arrow in the reaction graph, as in (4) or (9), which are found later in the paper.

B. Reaction Network within Interacting Compartments (RNIC)

We have already introduced the basic idea of the RNIC model in the introduction. Here we fill in the necessary technical details. We point the interested reader to Ref. 22 for a full mathematical introduction for the model. Note that the detailed choices we specify in this section, and especially in the pseudo-code provided at the end, are those that we make in our Matlab code for the simulation of these processes (and which is freely available).

As mentioned in the introduction, the RNIC model consists of interacting compartments, each of which contains an evolving copy of a given reaction network. Therefore, we begin by denoting the reaction network by

$$\mathcal{I} = \{\mathcal{S}, \mathcal{C}, \mathcal{R}\}.$$

When assuming stochastic mass-action kinetics, we will denote the set of rate constants by \mathcal{K} , and denote

$$\mathcal{I}_{\mathcal{K}} = \{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}.$$

Turning to the compartment model, the number of compartments is modeled as a stochastic reaction network as well. Specifically, by



with stochastic mass-action kinetics and where the rate constants have been placed next to the respective reaction arrows with κ_I the rate constant for inflows, κ_E for exits, κ_F for fragmentations, and κ_C for coagulations (following the terminology of Ref. 21 and Ref. 22). We will denote by $\mathcal{H}_{\mathcal{K}}$ the compartment reaction network (4) (where we have also expanded the set \mathcal{K} to include the rate constants for both the reaction network \mathcal{I} and the compartment model).

Denote by $M_C(t)$ the number of compartments at time $t \geq 0$. Then, following (1), the compartment model satisfies the stochastic equation

$$M_C(t) = M_C(0) + Y_I(\kappa_I t) - Y_E\left(\kappa_E \int_0^t M_C(s) ds\right) + Y_F\left(\kappa_F \int_0^t M_C(s) ds\right) - Y_C\left(\kappa_C \int_0^t M_C(s)(M_C(s) - 1) ds\right),$$

where Y_I, Y_E, Y_F , and Y_C are independent unit-rate Poisson processes.

Between the transition times of the Markov process M_C each compartment contains an independently evolving copy of the stochastic reaction network $\mathcal{I}_{\mathcal{K}}$. We numerically order the compartments and for $i \in \{1, \dots, M_C(t)\}$ we denote the state of the stochastic reaction network evolving in the i th compartment by $X_i(t)$. We now simply need to specify what happens to the model at the transition times of M_C . We do that below. We point out that all choices of random variables below are independent from each other and independent from the Poisson processes Y_I, Y_E, Y_F , and Y_C mentioned above.

We will assume that a transition for M_C takes place at time t . Hence, before the transition there are exactly $M_C(t-)$ compartments (where, again, $t-$ denotes a limit in t from the left). We now consider each of the four possible transition types for M_C . We note that the names of certain indices below, including IndexDel, IndexFrag, ri1, and ri2, are the names of the indices utilized in the Matlab code we are making available.

1. Case 1: a new compartment arrives at time t . In short, in this case we append a new compartment at the end of our list and initialize the stochastic reaction network via a probability distribution we denote by μ . Specifically, we do the following.

- (a) Set $M_C(t) = M_C(t-) + 1$.
 - (b) Set $X_i(t) = X_i(t-)$ for all $i \in \{1, \dots, M_C(t-)\}$ (that is, the reaction networks within each of the existing compartments remain the same).
 - (c) Initialize the stochastic reaction network of the new compartment. The state of the new compartment will be drawn from a fixed probability measure μ on $\mathbb{Z}_{\geq 0}^d$, where d is the number of species in the reaction network model \mathcal{I}_K .
2. Case 2: a compartment exits at time t . In short, in this case, we delete a compartment at random and shift the indices of the remaining compartments down appropriately. Specifically, we do the following.
- (a) Choose from $\{1, \dots, M_C(t-)\}$ uniformly; with the chosen index called IndexDel.
 - (b) For $i \in \{1, \dots, \text{IndexDel} - 1\}$, set $X_i(t) = X_i(t-)$.
 - (c) For $i \in \{\text{IndexDel}, \dots, M_C(t-) - 1\}$, set $X_i(t) = X_{i+1}(t-)$ (that is, we shift indices by 1).
 - (d) Set $M_C(t) = M_C(t-) - 1$.
3. Case 3: a compartment fragments into two at time t . In short, in this case, one compartment is chosen to divide. Each molecule of each species is chosen to either remain in the old compartment, or be placed into a new compartment numbered as $M_C(t-) + 1$. Specifically, we do the following.
- (a) Set $M_C(t) = M_C(t-) + 1$.
 - (b) Choose from $\{1, \dots, M_C(t-)\}$ uniformly, with the chosen index called IndexFrag.
 - (c) For each species $S_j \in \mathcal{S}$, we generate a binomial random variable with parameters $n = X_{\text{IndexFrag},j}(t-)$ (abundance of species S_j in compartment IndexFrag) and $p = 1/2$.
 - (d) The values given by the binomial random variables determine the state of $X_{\text{IndexFrag}}(t)$ (i.e., they are the molecules that remain).
 - (e) The state of $X_{M_C(t)}(t)$ is $X_{\text{IndexFrag}}(t-) - X_{\text{IndexFrag}}(t)$.
4. Case 4: a coagulation (merger). In short, in this case two compartments are chosen to merge. The contents are combined into one of the compartments and the other is deleted. Specifically, we do the following.

- (a) Choose two indices, $ri1, ri2 \in \{1, \dots, M_C(t-)\}$ uniformly, with $ri1 \neq ri2$.
- (b) Combine the contents into compartment $ri1$: $X_{ri1}(t) = X_{ri1}(t-) + X_{ri2}(t-)$.
- (c) Delete the compartment $ri2$ as detailed in Case 2 above.
- (d) Set $M_C(t) = M_C(t-) - 1$.

In agreement with Ref. 22, we will denote the stochastic process associated to the full RNIC model by F^{sim} (where the label “sim” denotes that this representation of the model is natural for simulations). Hence, $F^{\text{sim}}(t)$ determines $M_C(t)$ and each of $X_i(t)$, $i \in \{1, \dots, M_C(t)\}$, for each $t \geq 0$. The process F^{sim} is a continuous-time Markov chain with discrete state space $\bigcup_{m=0}^{\infty} (\mathbb{Z}_{\geq 0}^d)^m$, the space of finite tuples of $\mathbb{Z}_{\geq 0}^d$ (Lemma 2.5 in Ref.22). For example, if $d = 2$ and $M_C(t) = 3$ a possible realization of $F^{\text{sim}}(t)$ is

$$F^{\text{sim}}(t) = \left(\left[\begin{array}{c} 4 \\ 5 \end{array} \right], \left[\begin{array}{c} 0 \\ 10 \end{array} \right], \left[\begin{array}{c} 17 \\ 2 \end{array} \right] \right)$$

which would have $X_1(t) = \left[\begin{array}{c} 4 \\ 5 \end{array} \right]$, $X_2(t) = \left[\begin{array}{c} 0 \\ 10 \end{array} \right]$, and $X_3(t) = \left[\begin{array}{c} 17 \\ 2 \end{array} \right]$. When we wish to denote a parameterized family, we will once again append our processes with a θ : $F^{\text{sim},\theta}$, M_C^θ , and X_i^θ .

Having specified the model, we can present a pseudo-code for how to simulate a given RNIC process. In the pseudo-code below, we do not specify the algorithms being used to simulate M_C or the stochastic reaction networks within each compartment, as we leave that up to the implementer. Natural choices are the Gillespie algorithm^{12,13} or the next reaction method^{40,41}. These can both be found in Appendix B. We will denote the initial distribution of M_C by ν , the initial distribution for the initial compartments by μ_0 , and the initial distribution for compartments that arrive as μ . Note that it is possible, though not necessary, that $\mu_0 = \mu$.

Algorithm 1 (Pseudo-code for simulating an RNIC model, F^{sim}). *Given: a stochastic reaction network $\mathcal{I}_{\mathcal{K}}$, the compartment model (4), the parameters of the model \mathcal{K} , which consist of the rate constants $\{\kappa_k\}$ for $\mathcal{I}_{\mathcal{K}}$, the parameters of the compartment model $\{\kappa_I, \kappa_E, \kappa_F, \kappa_C\}$, and initial distributions ν , μ_0 , and μ .*

Repeat steps 4 – 8 until a stopping criteria is reached. All calls to random variables are independent from all others.

1. Determine $M_C(0)$ via ν .
2. For each $i \in \{1, \dots, M_C(0)\}$ determine $X_i(0)$ via μ_0 .
3. Set $t = 0$.
4. Using an exact simulation method (e.g., Gillespie's algorithm—Algorithm 4—or the next reaction method—Algorithm 5), determine the time Δ until the next transition of the compartment model, M_C .
5. Using an exact simulation method (e.g., Gillespie's algorithm—Algorithm 4—or the next reaction method—Algorithm 5), for each $i \in \{1, \dots, M_C(t)\}$ simulate X_i from time t to time $t + \Delta$.
6. Determine which type of transition occurs for the compartment model at time $t + \Delta$.
7. Update the model as detailed in the four cases listed above depending upon which type of transition takes place for the compartment model.
8. Set $t \leftarrow t + \Delta$.

III. METHODS FOR PARAMETRIC SENSITIVITIES

We provide a number of methods for the estimation of parametric sensitivities of RNIC models. In Section III A, we provide the (unbiased) Girsanov or Likelihood Ratio method in this setting. In Section III B we provide a number of coupling methods for the implementation of finite differences.

A. Likelihood Ratio, or Girsanov, transformation method

We provide the Likelihood Ratio method²³, often called the Girsanov transformation method in the biosciences²⁵, for the RNIC model when the perturbed parameters are rate constants for either the compartment model, $\mathcal{H}_{\mathcal{K}}$, or the chemical model $\mathcal{I}_{\mathcal{K}}$. There are other possible parameters to consider, such as any parameters associated with the distributions ν , μ_0 , or μ . However, those cases can be handled in a similar, and straightforward, manner.

While we do not provide formal mathematical justification for this method here (though we refer the interested reader to Refs. 23, 42, and 43) we do try to provide some intuition by explaining how the method works for the estimation $\frac{d}{d\theta} \mathbb{E}[f(X^\theta(t))]$, where X^θ is a standard

stochastic reaction network and t is some terminal time. Extension to the RNIC model is then relatively straightforward.

Consider a reaction network with intensity functions $\{\lambda_k^\theta\}$, which are parameterized by θ , and associated jump directions $\{\zeta_k\}$. Denote $\lambda_{\text{tot}}^\theta(x) = \sum_k \lambda_k^\theta(x)$. The key point for this method is that it proceeds by finding an appropriate function W^θ , often called the “weight function,” so that

$$\frac{d}{d\theta} \mathbb{E}[f(X^\theta(t))] = \mathbb{E}[f(X^\theta(t))W^\theta(t)].$$

One can then estimate the derivative via Monte Carlo with independent samples of $f(X^\theta(t))W^\theta(t)$.

The function W^θ is found by taking the derivative, with respect to the parameter θ , of the logarithm of the density of the process up to time t . For example, suppose that $X : [0, t] \rightarrow \mathbb{Z}_{\geq 0}^d$ is a particular path of the process (that one may have simulated, for example). Then, for this particular path, let $t_0 = 0$, $N(t)$ be the number of reactions that have taken place up to time t , t_i be the time of the i th transition (for $i \geq 1$), k_i^* be the index of the reaction type that takes place at time t_i , and $\Delta_i := t_{i+1} - t_i$ be the holding time in state X_{t_i} . Thinking in terms of the Gillespie algorithm, i.e., which reaction happens next and when that reaction takes place, which are a discrete event and an exponential holding time, respectively, it is then relatively straightforward to see^{23,25} that the density of the process at time $t \geq 0$ is proportional to

$$\begin{aligned} & \left(\prod_{i=1}^{N(t)} \underbrace{\frac{\lambda_{k_i^*}^\theta(X(t_{i-1}))}{\lambda_{\text{tot}}^\theta(X(t_{i-1}))}}_{\text{Which reaction}} \underbrace{\lambda_{\text{tot}}^\theta(X(t_{i-1})) e^{-\lambda_{\text{tot}}^\theta(X(t_{i-1})) \cdot \Delta_{i-1}}}_{\text{Exponential holding time}} \right) \cdot \underbrace{e^{-\lambda_{\text{tot}}^\theta(X(t_{N(t)}))(t-t_{N(t)})}}_{\text{No reaction from } t_{N(t)} \text{ to } t} \\ & = \left(\prod_{i=1}^{N(t)} \lambda_{k_i^*}^\theta(X(t_{i-1})) \right) e^{-\int_0^t \lambda_{\text{tot}}^\theta(X(s)) ds}. \end{aligned}$$

Taking logarithms and derivatives is now straightforward, and we have

$$W^\theta(t) = \sum_{i=1}^{N(t)} \frac{\frac{d}{d\theta} \lambda_{k_i^*}^\theta(X(t_{i-1}))}{\lambda_{k_i^*}^\theta(X(t_{i-1}))} - \int_0^t \frac{d}{d\theta} \lambda_{\text{tot}}^\theta(X(s)) ds.$$

Note that in the case of stochastic mass-action kinetics with $\theta = \kappa_j$, we have the simple expressions

$$\frac{\frac{d}{d\theta} \lambda_{k_i^*}^\theta(x)}{\lambda_{k_i^*}^\theta(x)} = \begin{cases} \frac{1}{\kappa_j} & \text{if } k_i^* = \kappa_j \\ 0 & \text{else} \end{cases}, \quad \text{and} \quad \frac{d}{d\theta} \lambda_{\text{tot}}^\theta(x) = \frac{1}{\kappa_j} \lambda_j^\theta(x).$$

We point out that in the case of mass-action kinetics the above terms are not defined when $\theta = 0$. Hence, the method is not valid in that case. An implementation of this method, when $\theta > 0$, is given in Algorithm 6 in Appendix B.

We now turn back to the RNIC model. We will denote our statistic of interest as $\mathbb{E}[f(F^{\text{sim},\theta}(t))]$, where $F^{\text{sim},\theta}(t)$ is the state of the RNIC model at time t and $f : \bigcup_{m=0}^{\infty} (\mathbb{Z}_{\geq 0}^d)^m \rightarrow \mathbb{R}$ is a function of interest. We will denote by W^θ the generated weight function. Hence, we utilize the algorithms below to estimate $\frac{\partial}{\partial \theta} \mathbb{E}[f(F^{\text{sim},\theta}(t_{\text{end}}))]$ by averaging the independent realizations $f(F_{[\ell]}^{\text{sim},\theta}(t_{\text{end}}))W_{[\ell]}^\theta(t_{\text{end}})$, with $[\ell]$ enumerating the independent calls to the algorithm.

In fact, the details above pertaining to the Girsanov method for standard stochastic reaction networks allow us to immediately provide the Girsanov transformation method when the perturbed parameter is one of the rate constants associated with the compartment model, $\mathcal{H}_\mathcal{K}$. This is because the compartment model can be simulated with no knowledge of the internal reaction networks. Specifically, the following pseudo-algorithm works:

1. Utilize Algorithm 6, the standard Girsanov method, to simulate the compartment model.
2. In between compartment events, simulate the independently evolving reaction networks as in Step 5 of Algorithm 1.

We turn to the case when the parameter of interest is in the reaction network $\{\mathcal{I}_\mathcal{K}\}$. Because the reaction networks within each compartment evolve independently, we may sum the representative weight functions from the calls to $\mathcal{I}_\mathcal{K}$ between compartment events. Hence, simulation in this case is also straightforward. However, since this situation is different from what is standard, we provide a pseudo-algorithm.

Algorithm 2 (Girsanov transformation method if the perturbed parameter is from the reaction network model, $\mathcal{I}_\mathcal{K}$). *Given: a stochastic reaction network $\mathcal{I}_\mathcal{K}$, the compartment model (4), the parameters of the model \mathcal{K} , which consist of the rate constants $\{\kappa_k\}$ for $\mathcal{I}_\mathcal{K}$ and the parameters of the compartment model $\{\kappa_I, \kappa_E, \kappa_F, \kappa_C\}$, initial distributions ν , μ_0 , and μ .*

All calls to random variables are independent from all others.

1. Determine $M_C(0)$ via ν .

2. For each $i \in \{1, \dots, M_C(0)\}$ determine $X_i(0)$ via μ_0 .
3. Set $W^\theta = 0$ and set $t = 0$.
4. Using Gillespie's Algorithm 4, determine the time Δ until the next transition of the compartment model, M_C .
5. If $t + \Delta \geq t_{end}$, set $\Delta = t_{end} - t$ and break after step 6.
6. Using the reaction network Girsanov transformation Algorithm 6, for all $i \in \{1, \dots, M_C(t)\}$ simulate X_i from time t to time $t + \Delta$ and let W_i denote the output weight function.
Set $W^\theta \leftarrow W^\theta + \sum_{i=1}^{M_C(t)} W_i^\theta$.
7. Determine which type of transition occurs for the compartment model at time $t + \Delta$.
8. Update the RNIC model as detailed in the four cases listed in Section II B depending upon which type of transition takes place for the compartment model.
9. Set $t \leftarrow t + \Delta$.

Output $F^{\text{sim},\theta}(t)$ and W^θ .

B. Finite difference methods

As detailed in Appendix A, the basic idea of finite difference methods is to use the following straightforward approximation,

$$\begin{aligned} \frac{d}{d\theta} \mathbb{E}[f(F^{\text{sim},\theta}(t))] &\approx \frac{\mathbb{E}[f(F^{\text{sim},\theta+h}(t)) - f(F^{\text{sim},\theta}(t))]}{h} \\ &\approx \frac{1}{n} \sum_{\ell=1}^n \frac{1}{h} \left(f(F_{[\ell]}^{\text{sim},\theta+h}(t)) - f(F_{[\ell]}^{\text{sim},\theta}(t)) \right), \end{aligned} \quad (5)$$

(or a centered difference) where the key fact is that $F_{[\ell]}^{\text{sim},\theta+h}$ and $F_{[\ell]}^{\text{sim},\theta}$ are generated on the same probability space. Specifically, we want $F_{[\ell]}^{\text{sim},\theta+h}$ and $F_{[\ell]}^{\text{sim},\theta}$ to be coupled so that $\text{Var} \left(f(F_{[\ell]}^{\text{sim},\theta+h}(t)) - f(F_{[\ell]}^{\text{sim},\theta}(t)) \right)$ is reduced.⁴⁴

We will use five basic coupling methods, each with different “flavors” depending on what type of parameter is being perturbed. We begin with a simple introduction to each.

Method 1: Independent Samples. This is straightforward. With this method, the processes are generated independently. This should be viewed as the base case. †

Method 2: Common Random Variables (CRV). This is nearly as simple as generating the processes independently and consists of simply reusing the seed of the random number generator for the calls to the different processes. Alternatively, and equivalently, vectors of uniform $[0, 1]$ —or other—random variables that can be used to simulate the process can be pre-generated. This is simply an implementation choice and not a theoretical constraint. ‡

Method 3: Common Reaction Path (CRP). This method was developed for standard stochastic reaction networks, so we explain it in that language. Hence, consider a stochastic reaction network with jump directions $\{\zeta_k\}$ and intensity functions $\{\lambda_k^\theta\}$, which are parameterized by θ . The Common Reaction Path method for such a process couples X^θ and $X^{\theta+h}$ by sharing the unit-rate Poisson processes in (2), see Ref. 32. That is, X^θ and $X^{\theta+h}$ are coupled (generated) in the following manner,

$$\begin{aligned} X^{\theta+h}(t) &= X^{\theta+h}(0) + \sum_k Y_k \left(\int_0^t \lambda_k^{\theta+h}(X^{\theta+h}(s)) ds \right) \zeta_k \\ X^\theta(t) &= X^\theta(0) + \sum_k Y_k \left(\int_0^t \lambda_k^\theta(X^\theta(s)) ds \right) \zeta_k, \end{aligned}$$

where the key point is that the same unit-rate Poisson processes, $\{Y_k\}$, are utilized for both X^θ and $X^{\theta+h}$. We will often refer to this as the classical CRP method in order to differentiate it from the local-CRP method introduced next. ‡

Method 4: local Common Reaction Path (local-CRP). We again explain this method in the context of standard stochastic reaction networks, using the same notation as above (i.e., jump directions $\{\zeta_k\}$ and intensity functions $\{\lambda_k^\theta\}$). The idea of the local-CRP coupling, as introduced in Ref. 33, is to discretize your time interval $[0, T]$ into multiple sub-intervals and for each such subinterval generate the coupled processes using a new set of independent unit-rate Poisson processes. That is, use the classical CRP coupling mentioned above within each sub-interval, with new Poisson processes.

More formally, we begin by discretizing an interval of time $[0, T]$ by letting $\pi = \{0 = s_0 < s_1 < \dots < s_r = T\}$. Then, let $\{Y_{km}, \text{ for } k \in \{1, \dots, R\}, m \in \{0, 1, 2, \dots\}\}$ be a set of independent, unit-rate Poisson processes, where R is the number of reactions (i.e., the size of the set \mathcal{R}). Then, the local-CRP coupling over $[0, T]$ with respect to π is the solution to

$$X^{\theta+h}(t) = X^{\theta+h}(0) + \sum_{k=1}^R \sum_{m=0}^{\infty} Y_{km} \left(\int_{t \wedge s_m}^{t \wedge s_{m+1}} \lambda_k^{\theta+h}(X^{\theta+h}(s)) ds \right) \zeta_k$$

$$X^{\theta}(t) = X^{\theta}(0) + \sum_{k=1}^R \sum_{m=0}^{\infty} Y_{km} \left(\int_{t \wedge s_m}^{t \wedge s_{m+1}} \lambda_k^{\theta}(X^{\theta}(s)) ds \right) \zeta_k.$$

We note here that in the implementations utilized in this paper, the discretization time points $\{s_i\}$ will themselves be random. ‡

Method 5: Split Coupling (SC). As with the two methods above, we again explain this method in the context of standard stochastic reaction networks, using the same notation as above (i.e., jump directions $\{\zeta_k\}$ and intensity functions $\{\lambda_k^{\theta}\}$). The Split Coupling method for such a process couples X^{θ} and $X^{\theta+h}$ by constructing them in the following manner^{26,34},

$$X^{\theta+h}(t) = X^{\theta+h}(0) + \sum_k Y_{k,1} \left(\int_0^t \min\{\lambda_k^{\theta+h}(X^{\theta+h}(s)), \lambda_k^{\theta}(X^{\theta}(s))\} ds \right) \zeta_k$$

$$+ \sum_k Y_{k,2} \left(\int_0^t \lambda_k^{\theta+h}(X^{\theta+h}(s)) - \min\{\lambda_k^{\theta+h}(X^{\theta+h}(s)), \lambda_k^{\theta}(X^{\theta}(s))\} ds \right) \zeta_k$$

$$X^{\theta}(t) = X^{\theta}(0) + \sum_k Y_{k,1} \left(\int_0^t \min\{\lambda_k^{\theta+h}(X^{\theta+h}(s)), \lambda_k^{\theta}(X^{\theta}(s))\} ds \right) \zeta_k$$

$$+ \sum_k Y_{k,3} \left(\int_0^t \lambda_k^{\theta}(X^{\theta}(s)) - \min\{\lambda_k^{\theta+h}(X^{\theta+h}(s)), \lambda_k^{\theta}(X^{\theta}(s))\} ds \right) \zeta_k,$$
(6)

where $\{Y_{k,1}, Y_{k,2}, Y_{k,3}\}$ are all independent unit-rate Poisson processes. Note that both processes share the jump processes associated with the Poisson processes $\{Y_{k,1}\}$. For the purposes of this paper, we will simply note that the Split Coupling works (in that X^{θ} and $X^{\theta+h}$ have the correct distributions) because of the fact that Poisson processes are additive in that if Y_1, Y_2 , and Y_3 are unit-rate Poisson processes, Y_1 and Y_2 are independent, and if λ_1, λ_2 are integrable functions, then $Y_1(\int_0^t \lambda_1(s) ds) + Y_2(\int_0^t \lambda_2(s) ds)$ is equal in distribution to $Y_3(\int_0^t (\lambda_1(s) + \lambda_2(s)) ds)$. ‡

The question now is how we implement these basic methods in the RNIC setting. There are two distinct cases to consider: whether the parameter being perturbed is a compartment parameter ($\kappa_I, \kappa_E, \kappa_F$, or κ_C) or is a parameter from the reaction network (e.g., a rate constant for stochastic mass-action kinetics). One case is demonstrably more straightforward, and so we start with that.

Case 1: θ is a parameter of the reaction network, \mathcal{I} .

In this case the compartment model (4), whose transitions and rates do not depend upon the states of the chemical systems, can be shared between $F^{\text{sim},\theta}$ and $F^{\text{sim},\theta+h}$. Hence, only a slight modification to Algorithm 1 is needed. We provide that modification here assuming a Gillespie implementation for the simulation of the compartments. We also utilize only the local-CRP below as opposed to the classical CRP.

Algorithm 3 (Generic coupling for an RNIC model when perturbed parameter is from the reaction network, \mathcal{I}). *Given: a reaction network \mathcal{I} with jump directions $\{\zeta_k\}$ and intensity functions λ_k^θ , the compartment model (4) with parameters $\{\kappa_I, \kappa_E, \kappa_F, \kappa_C\}$, initial distributions ν , μ_0 , and μ .*

All calls to random variables are independent from all others.

1. Determine $M_C(0)$ via ν .
2. For each $i \in \{1, \dots, M_C(0)\}$ determine $X_i^\theta(0)$ via μ_0 and set $X_i^{\theta+h}(0) = X_i^\theta(0)$.
3. Set $t = 0$.
4. Using Gillespie's Algorithm 4, determine the time Δ until the next transition of the compartment model, M_C .
5. If $t + \Delta \geq t_{\text{end}}$, set $\Delta = t_{\text{end}} - t$ and break after step 6.
6. Using one of independent samples, the CRV coupling, the local-CRP coupling or the Split Coupling, for each $i \in \{1, \dots, M_C(t)\}$ simulate X_i^θ and $X_i^{\theta+h}$ from time t to time $t + \Delta$. Note the following.
 - For independent realizations, this step amounts to making two independent calls to an exact simulation method, as can be found in Appendix B.
 - For the CRV method, this step consists of generating a new seed for each compartment and using that seed for both calls to the exact simulation method. Equivalently, one can simply pass a given vector of random variables to each of the two calls of an exact simulation method, and use those random variables to construct the processes. We chose the latter option of passing a vector of random variables and note that this is an implementation choice, as opposed to a theoretical constraint.

- For the local-CRP method, this step consists of generating new unit-rate Poisson processes for each reaction type in each compartment (via a sequence of independent unit-rate exponentials) and utilizing those Poisson processes to separately construct both X_i^θ and $X_i^{\theta+h}$ on $[t, t + \Delta]$.
 - For the Split Coupling, this step simply consists of simulating (6) within each compartment. This can be done in a straightforward manner via Gillespie's algorithm (since (6) is also a Markov process) or the next reaction method^{26,34}.
7. Determine which type of transition occurs for the compartment model at time $t + \Delta$.
 8. Update the RNIC model as detailed in the four cases listed in Section II B depending upon which type of transition takes place for the compartment model. (See below for more details.)
 9. Set $t \leftarrow t + \Delta$, and return to step 4.

Output $F^{\text{sim},\theta}(t_{\text{end}})$ and $F^{\text{sim},\theta+h}(t_{\text{end}})$.

Remark 1. It is worth delving a bit into step 8 above in order to ensure that the coupling is as tight as possible, with special focus on when a fragmentation event takes place. We do the following for all of our simulations. There are, of course, four cases: one for each of the possible compartment events.

1. If the transition of the compartment model is an arrival, then the new compartment is initialized via μ once and that value is assigned to both the θ process and the $\theta + h$ process.
2. If the transition of the compartment model is departure/exit, then the compartment deleted is the same for both processes.
3. If the transition of the compartment model is a coagulation (merger), then the two compartments that merge are the same for both the θ and $\theta + h$ process. Moreover, the choice of which of the two is deleted (and which collects the material) is also the same.
4. If the transition of the compartment model is a fragmentation, then the compartment chosen for splitting is the same for both processes. However, how the contents of the

chosen compartment are divided should be considered carefully. For example, in our single-path simulations our splitting rule is the following: each molecule of each species will choose its compartment via a fair coin flip. Therefore, when generating a single path (i.e., no coupling) we may simply do the following: for each species, generate a binomial random variable with parameters $m = \#$ of that species present in the chosen compartment and $p = 1/2$. However, for our coupled processes it is possible (and even likely) that the compartment chosen will have different numbers of each species for the θ and $\theta + h$ processes. Because of this, we suggest (and carry out) the following.

Suppose it is the i th compartment chosen for fragmentation and the j th species has abundances $X_{i,j}^\theta$ and $X_{i,j}^{\theta+h}$, respectively. Suppose further that $X_{i,j}^\theta \leq X_{i,j}^{\theta+h}$ (with a symmetric construction in the other case). Then, for the θ process, we choose a binomial random variable with parameters $m = X_{i,j}^\theta$ and $p = 1/2$. Call that value M_1 . For the $\theta + h$ process, we choose a binomial random variable with parameters $M_2 = X_{i,j}^{\theta+h} - X_{i,j}^\theta$ and $p = 1/2$, and then add that value to M_1 . We carry out that basic idea for each $j \in \{1, \dots, d\}$. In this manner, we have coupled the splitting (and therefore hopefully the processes) as tightly as possible. \square

We make one further comment regarding the use of the local-CRP method versus the classical CRP method. We noted explicitly above that when the local-CRP method is being used, new unit-rate Poisson processes are to be utilized for each reaction network between each transition of the compartment model. This is done for practical purposes: since the compartments are constantly merging, fragmenting, etc., if the classical CRP method were to be used it would be unclear which Poisson processes go with which compartment. Hence, the local-CRP is more natural to use in this setting. In Ref. 33, it was proven that as the number of replacements of the Poisson processes increases, the coupled processes converge in distribution to the coupled processes generated via the Split Coupling. We will see this play out in our examples of Section IV and it explains why the variance of the local-CRP method, as we have implemented it, closely matches that of the Split Coupling in the RNIC setting.

Case 2: θ is a parameter of the compartment model \mathcal{H} .

Now the compartment processes M_C^θ and $M_C^{\theta+h}$ eventually diverge and the two processes

$F^{\text{sim},\theta}$ and $F^{\text{sim},\theta+h}$ can no longer share the compartment model. We cover the various coupling strategies in this case.

Independent samples. We generate the process $F^{\text{sim},\theta}$ via Algorithm 1, change the parameter, and generate the process $F^{\text{sim},\theta+h}$ via Algorithm 1. The processes are constructed independently.

Common Random Variables. We fix a seed of the random number generator we have not used as of yet. We generate the process $F^{\text{sim},\theta}$ via Algorithm 1, change the parameter, and generate the process $F^{\text{sim},\theta+h}$ via Algorithm 1 using the same seed.

Classical CRP. We only couple the processes $F^{\text{sim},\theta}$ and $F^{\text{sim},\theta+h}$ via the compartments (utilizing the classical CRP method of Ref. 32) and the compartment events. We do not couple the stochastic reaction networks taking place within the compartments between the events (see Remark 2 for why). Note that to couple the processes as tightly as possible, we need to send multiple vectors of random variables for the generation of our two processes: one or more vectors for each possible compartment event that can take place, as well as the needed Poisson processes for the compartment model. Specifically, we generate the following random variables and processes and use them to generate both $F^{\text{sim},\theta}$ and $F^{\text{sim},\theta+h}$:

- The Poisson processes Y_I, Y_E, Y_C, Y_F (generated as a vector of unit-exponentials);
- A vector of uniform[0,1] random variables to determine the initial values of the compartments (both at time 0 and those that arrive);
- A vector of uniform[0,1] random variables to determine which compartment is chosen for deletions;
- A vector of uniform[0,1] random variables to determine which compartments coagulate;
- A vector of uniform[0,1] random variables to determine which compartment fragments;
- A vector of uniform[0,1] random variables to determine the needed binomial random variables for a fragmentation event.

These vectors of random variables are utilized in the obvious way, but we point to the freely available Matlab code for precise details.

Split Coupling. We couple the compartment models M_C^θ and $M_C^{\theta+h}$ using the split coupling. Events that take place using the split coupling can be “shared” (which occurs when

one of the counting processes associated to $Y_{k,1}$ in (6) takes place—these have intensity functions that are the minimum of the two individual intensity functions) or not. If the event is not shared, then one simply updates the relevant compartment model (either M_C^θ or $M_C^{\theta+h}$) as usual. If the event is shared, then the following procedures are followed:

1. If the event is an arrival, both new compartments are initialized from μ with the same value.
2. If the event is a deletion, the same uniform[0,1] random variable is used to determine which compartment is deleted. Note that this does not necessarily mean the processes will delete the same numbered compartment.
3. If the event is a coagulation, the same uniform[0,1] random variables are used to determine which compartments merge for the two processes.
4. If the event is a fragmentation, the same uniform[0,1] random variable is used to determine which compartment fragments. Moreover, we utilize the same procedure for fragmentation that was detailed in point 4 of Remark 1.

We point the reader to the freely available Matlab code for the specific implementation.

When using the split coupling for the compartment model, compartment events take place simultaneously for the two processes $F^{\text{sim},\theta}$ and $F^{\text{sim},\theta+h}$. Hence, we are also able to use the split coupling for the chemical processes, $\{X_i^\theta\}$ and $\{X_i^{\theta+h}\}$ between such events (as in the case when a chemical parameter is being perturbed). Specifically, we couple the chemical processes sequentially as much as possible. That is, we generate

$$(X_1^\theta, X_1^{\theta+h}), \dots, (X_m^\theta, X_m^{\theta+h}), \quad \text{where } m = \min\{M_C^\theta, M_C^{\theta+h}\},$$

using the split coupling. Then, for any other compartments (for example, if $M_C^\theta > M_C^{\theta+h}$) we simply generate those paths independently.

We will also later provide results for when we use the Split Coupling on the compartment model (as detailed above) but *not* for the chemical models. In that case, we generate the processes $\{X_i^\theta\}$ and $\{X_i^{\theta+h}\}$ independently. We do this solely to compare with the CRP method (in which coupling of the chemical models is also not done).

Remark 2. Note that the local CRP method was not included in the list of coupling strategies used in this case. The reasons for this are as follows. Because θ is assumed to

be a compartment parameter, the timing of the compartment events of the processes $F^{\text{sim},\theta}$ and $F^{\text{sim},\theta+h}$ will not necessarily be equal. In fact, after the first compartment event that is associated with the perturbed parameter takes place for one of $F^{\text{sim},\theta}$ or $F^{\text{sim},\theta+h}$, the two compartment processes do not have any simultaneous compartment events for exits, fragmentations, or coagulations ever again (they will always share input events, since that rate is state-independent). Moreover, because the processes $F^{\text{sim},\theta}$ and $F^{\text{sim},\theta+h}$ are generated separately there is no way for the process $F^{\text{sim},\theta}$ to “know” when there is a compartment event for $F^{\text{sim},\theta+h}$, and vice-versa. Combining the above two points, there is no way for either process to “know” when a compartment event for the other took place, and so there is no way to update the Poisson processes for the chemical system at those times in a shared manner. Using the language of stochastic processes, the issue being pointed out here stems from the fact that while the CRP method produces two paths, those coupled paths are not Markovian.

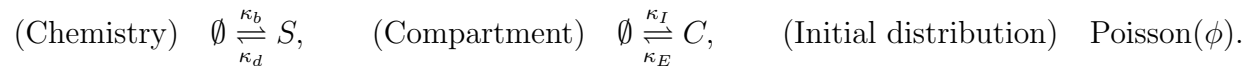
Theoretically, a way around this problem would be to generate the compartment models for $F^{\text{sim},\theta}$ and $F^{\text{sim},\theta+h}$ simultaneously from Y_I, Y_E, Y_F , and Y_C , while tracking all information used by each process. However, this would entail a large infrastructure in order to keep track of how much of the various Poisson processes Y_I, Y_E, Y_F , and Y_C each of $F^{\text{sim},\theta}$ and $F^{\text{sim},\theta+h}$ has seen by a given time and various vectors accounting for “future” information. This would be quite cumbersome and, potentially, quite slow. Moreover, we know from the analysis Ref. 33 that the resulting variance would be nearly identical to that of the Split Coupling (which does not require this added machinery). Hence, we choose not to perform this implementation. \square

IV. EXAMPLES

We provide two RNIC models as test cases for the various methods outlined above. For each model, we perturb both a chemical parameter and a compartment parameter. For the second model we also consider the situation in which more than one parameter is perturbed. All of the computations reported in this section were performed using Matlab version 2024b on a 2019 MacBook Pro using a 2.3 GHz 8-Core Intel I9 processor.

Example 2. Birth and death. Our first model is one of the simplest RNIC models, though it presents a nice test case that is also analytically tractable. The model consists of a

chemical system that is a birth and death process (termed an $M/M/\infty$ queue in the queueing literature) and a compartment model that is also a birth and death process. Specifically, we have the following:



Hence, both the fragmentation (κ_F) and coagulation (κ_C) parameters for the compartment model are set to zero, and so the compartments themselves do not interact. This model was considered as an example RNIC model in Ref. 21 and the chemical portion was utilized as an example in Ref. 26, where the split coupling was introduced in the context of parametric sensitivity analysis. Following Ref. 21, we will take the rate constants for the chemical model to be $\kappa_b = 1$ and $\kappa_d = 0.1$ and for the compartment model to be $\kappa_I = 1$ and $\kappa_E = 0.01$. Also following Ref. 21, we set $\phi = 10$, so that compartments arrive in equilibrium⁴⁵. We initialize the RNIC model itself with zero compartments. Denote by $S_{tot}(t)$ the total number of S molecules summed over the compartments at time t . We will estimate

$$\frac{d}{d\kappa_b} \mathbb{E}[S_{tot}(t)] \quad \text{and} \quad \frac{d}{d\kappa_E} \mathbb{E}[S_{tot}(t)].$$

This model lends itself to analysis, which makes it particularly useful in our study. By Ref. 46, we know that the stationary distribution is Poisson with mean 100. In fact, more can be determined. Denote by $\bar{c}(t)$ the mean value for the number of compartments at time $t \geq 0$. By Ref. 47, the distribution of the compartment process at time $t \geq 0$ is Poisson with a mean given by the solution to the ODE $\frac{d}{dt} \bar{c}(t) = \kappa_I - \kappa_E \bar{c}(t)$. By equation (19) in Ref. 21 the equations governing the means of the compartments and the total amount of S are

$$\begin{aligned} \frac{d}{dt} \bar{c}(t) &= \kappa_I - \kappa_E \bar{c}(t) \\ \frac{d}{dt} \mathbb{E}[S_{tot}(t)] &= \kappa_I \phi - \kappa_E \mathbb{E}[S_{tot}(t)] + \kappa_b \bar{c}(t) - \kappa_d \mathbb{E}[S_{tot}(t)]. \end{aligned} \tag{7}$$

These linear ODEs can be solved quite easily and so can be used to provide us with the exact values of the sensitivities and, importantly for us, the precise biases of the finite difference methods. We do not provide the solutions here explicitly as they are trivial to compute with any software package (e.g., Maple, Mathematica, etc.) but take up quite a bit of space.

Estimation of $\frac{d}{d\kappa_b} \mathbb{E}[S_{tot}(t)]$. Since κ_b is a parameter of the chemical model, we utilize Algorithm 2 for the Girsanov method and Algorithm 3 for the finite difference methods. The solution to $\mathbb{E}[S_{tot}(t)]$ given by the equations (7) has the general form $g_1(t) + \kappa_b g_2(t)$, for

functions g_1 and g_2 , which depend on rate constants other than κ_b . Hence, the dependence is linear in κ_b and the finite difference methods are *unbiased* estimators for $\frac{d}{d\kappa_b}\mathbb{E}[S_{tot}(t)]$. Thus, only the variances of the different methods need to be considered. Moreover, because the finite difference methods are unbiased, we chose to utilize the forward difference as opposed to the centered difference (see Appendix A), but this choice is immaterial.

For each of the finite difference methods, we utilized $n = 1,000$ paths to estimate the derivative. For the finite difference methods, each “path” consists of a realization of the coupled processes $(F^{\text{sim},\theta+h}, F^{\text{sim},\theta})$ (therefore, we end with 1,000 copies of each of $F^{\text{sim},\theta}$ and $F^{\text{sim},\theta+h}$). Moreover, we used a perturbation of $h = 1/10$, which is 10% of the parameter value. For the Girsanov method, we utilized 2,000 paths, which yields a similar computational budget to the finite difference methods.

In Figure 1 we report the estimator variances

$$\frac{\text{Var}(f(F^{\text{sim},\theta}(t)) \cdot W(t))}{n} \quad \text{and} \quad \frac{\text{Var}(f(F^{\text{sim},\theta+h}(t)) - f(F^{\text{sim},\theta}(t)))}{hn}, \quad (8)$$

for the Girsanov and finite difference methods, respectively, where f is the function that returns “Total S”, or S_{tot} , and W is the weight function for the Girsanov method. We explicitly point out that the Split Coupling and the local-CRP method have nearly identical estimator variances (as predicted from Ref. 33), and both variances are substantially lower than the other methods. We also note that, for the sake of comparison, we have provided two methods not detailed in the previous section: the use of independent samples and Common Random Variables that do not share the compartment model (making these the most naive methods possible). We do so to be able to visualize the benefit of coupling through the compartments, which is substantial.

We provide in Table I the time required to generate the paths for each of the methods. Since the time required for each method depends intimately on the hardware and software used and on the particulars of the implementation, it is sometimes difficult to interpret and could possibly be improved, perhaps dramatically, by clever implementations. Hence, we also provide in Table I the number of random variables used in the whole computation (but we do *not* include those random variables generated but not used by the computation in the local-CRP method). The number of random variables used is largely independent of implementation and can be taken as a (rough) proxy for the overall computational complexity. Figure 1 and Table I together paint a clear picture: for this particular problem, the Split

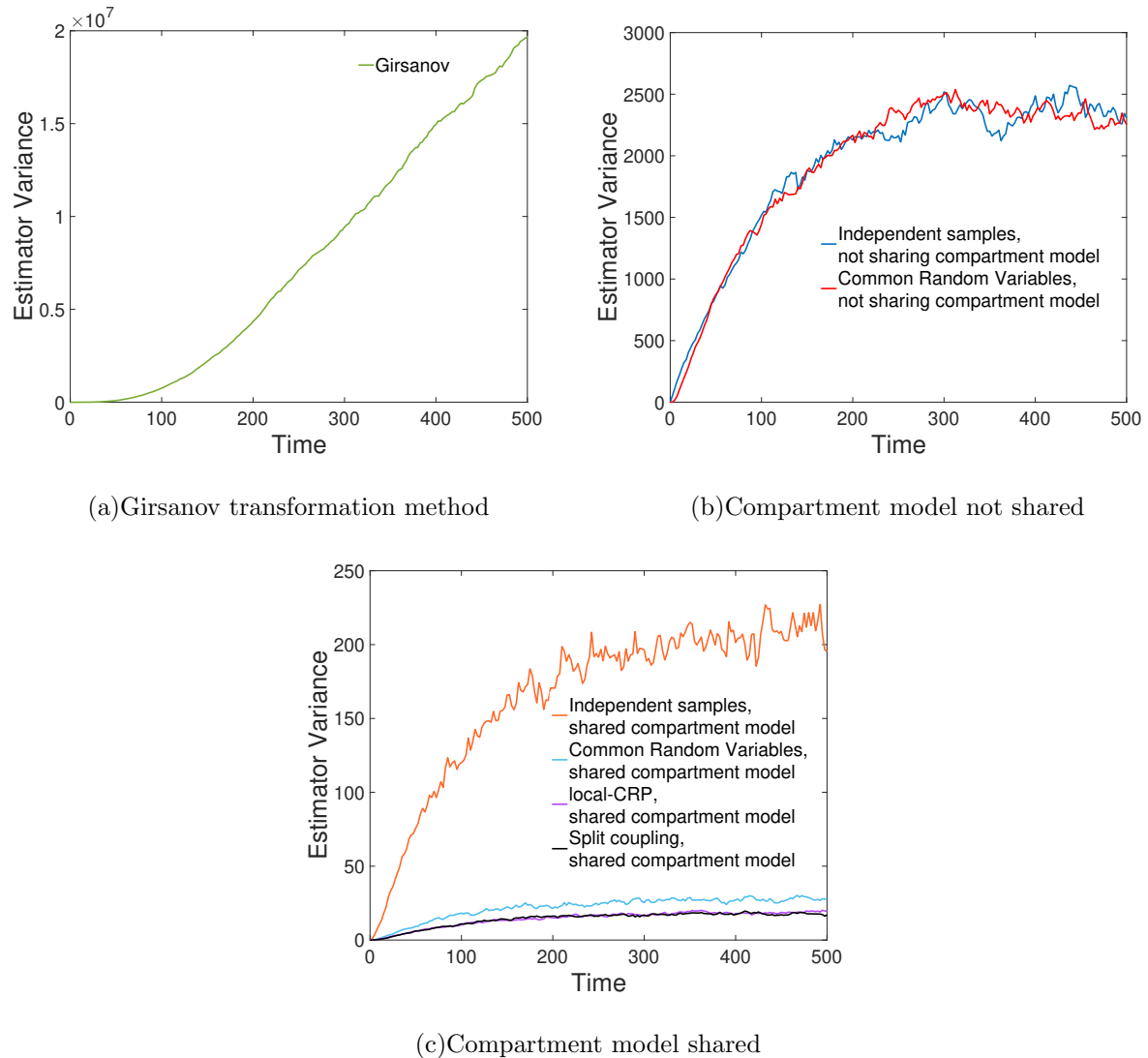


FIG. 1. Estimator variances (8) for $\frac{d}{d\kappa_b}\mathbb{E}[S_{tot}(t)]$ using various methods. For the (forward) finite difference methods, we used a perturbation of $h = 1/10$ and $n = 1,000$ coupled paths. For the Girsanov method we used $n = 2000$ paths. Note the vastly different scales on the y -axis.

Coupling is the most efficient.

Estimation of $\frac{d}{d\kappa_E}\mathbb{E}[S_{tot}(t)]$. As κ_E is a parameter of the compartment model, there is no longer the possibility of sharing the compartment model. Hence, we utilize the classical CRP method instead of the local-CRP method.

We may again utilize the equations (7) to calculate the desired sensitivity and the biases for the finite difference methods. Over the time frame of interest, $t \in [0, 500]$, the sensitivity starts at zero and decreases to $-90,000$ (image not shown here, but is easily generated with

Method	Time	RVs used
Girsanov	128 seconds	5.1×10^8
Independent samples, not sharing compartment model	129 seconds	5.2×10^8
Common Random Variables, not sharing compartment model	126 seconds	5.2×10^8
Independent samples, shared compartment model	111 seconds	5.2×10^8
Common Random Variables, shared compartment model	167 seconds	5.2×10^8
local-CRP, shared compartment model	299 seconds	5.3×10^8
Split Coupling, shared compartment model	118 seconds	2.7×10^8

TABLE I. Simulation times for the various methods for the estimation of $\frac{d}{d\kappa_b} \mathbb{E}[S_{tot}(t)]$. $n = 1,000$ coupled paths were used for the finite difference methods and $n = 2,000$ paths were used for the Girsanov method.

Maple, Mathematica, or Matlab). If we use a perturbation of $h = 1/1000$, which is again 10% of the nominal parameter value $\kappa_E = 1/100$, with a forward finite difference, then the bias ranges from zero (at time $t = 0$) to around 8,000 (at time $t = 500$). A centered difference provides a bias that ranges from 0 to approximately 180. This is a good approximation and so we choose that value for h combined with the centered finite difference.

We once again simulated $n = 1,000$ paths of the processes in the case of finite differences and $n = 2,000$ paths for the Girsanov method. See Figure 2 for the estimator variances of the various methods. The Split Coupling provides, by far, the lowest variance. The CRP method required 155 CPU seconds and 4.9×10^8 random variables to make the computation. The times required and numbers of random variables used for the other methods were all essentially the same to those in the previous case (for the estimation of $\frac{d}{d\kappa_b} \mathbb{E}[S_{tot}(t)]$) and reported in Table I. Hence, we do not bother to reproduce those numbers. The resulting estimator variance for the Split Coupling maxes out at around 3.5×10^5 , yielding an estimator standard deviation of around 591, which is a reasonable value given a bias of 180. \square

Example 3 (Genetic model with coagulation). Our second example has a chemistry that consists of transcription, translation, and dimerization of the resulting protein. This partic-

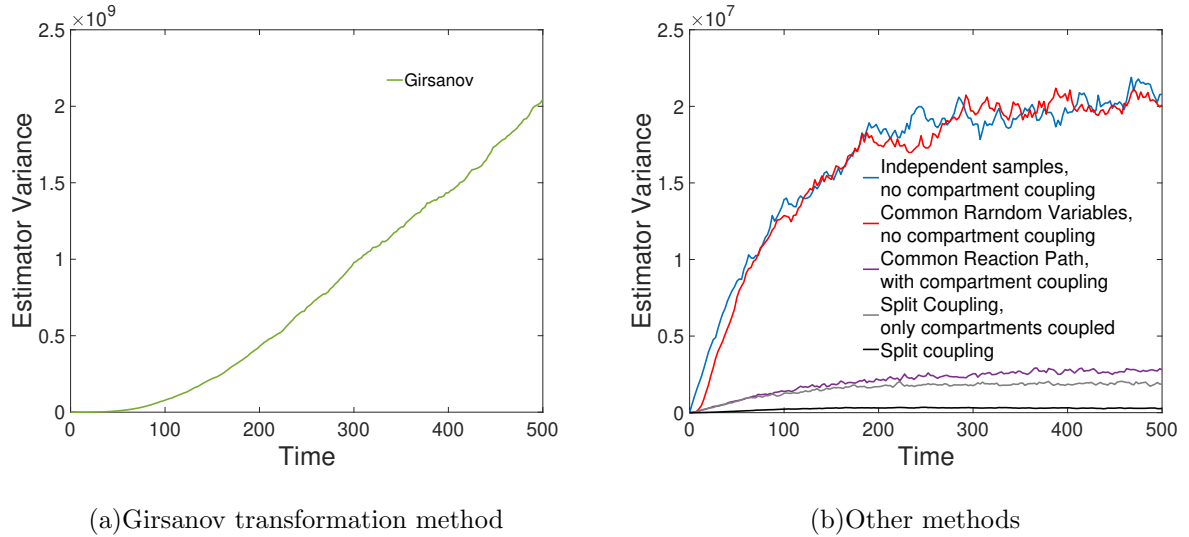
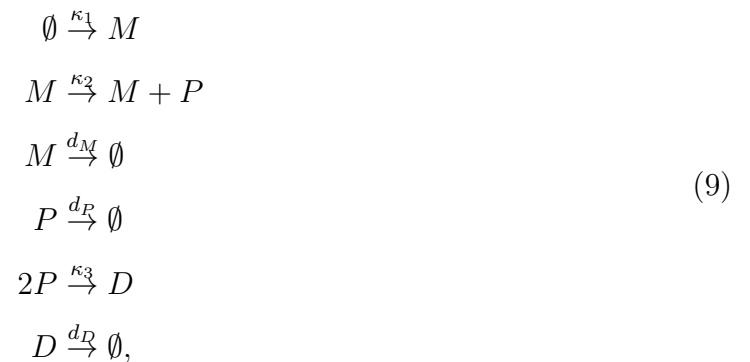
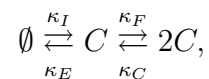


FIG. 2. Estimator variances (8) for $\frac{d}{d\kappa_E}\mathbb{E}[S_{tot}(t)]$ using various methods. For the (centered) finite difference methods, we used a perturbation of $h = 1/1000$ and $n = 1,000$ coupled paths. For the Girsanov method we used $n = 2000$ paths. Note that the Split Coupling, with both the compartment model and chemistry model being coupled, as detailed at the end of Section III B, has by far the lowest variance and is also the fastest (and utilizes the fewest random variables).

ular model is Example 2.4 in Ref. 11, and consists of the following set of reactions



with $\kappa_1 = 200$, $\kappa_2 = 10$, $d_M = 25$, $d_P = 1$, $\kappa_3 = 0.01$, and $d_D = 1$. We will assume that each cell/compartments has one gene, and so we suppress that species. Hence, this is a three species model with $\mathcal{S} = \{M, P, D\}$. For the compartment model, we have



with $\kappa_I = 10$, $\kappa_E = 3.5$, $\kappa_F = 3$, and $\kappa_C = 0.1$. We will initialize the RNIC model with a single compartment with zero copies of each species. Moreover, we will initialize each

compartment that appears with a reaction network with zero copies of each species. Finally, we will use our methods to estimate

$$\frac{d}{d\kappa_2}\mathbb{E}[\text{Total dimers}] \quad \text{and} \quad \frac{d}{d\kappa_F}\mathbb{E}[\text{Total dimers}],$$

where ‘‘Total dimers’’ is the sum of the number of dimers across all compartments.

Unlike the previous model, this RNIC model is not amenable to analysis. For the parameters chosen, the compartment model has a limiting mean of approximately 7.4 compartments (plots not shown). However, the fluctuations around this mean can be pronounced. In Figure 3, we provide a single realization of the compartment process.

Estimation of $\frac{d}{d\kappa_2}\mathbb{E}[\text{Total dimers}]$. Because the process is not amenable to analysis (which, of course, is the standard situation when one is using simulation and Monte Carlo), we must choose an h for our finite difference methods that we believe limits our bias sufficiently. For the parameter κ_2 , we chose to use a centered finite difference with $h = 1/10$, which is 1% of the nominal value of 10. We chose this by observing the behavior of the estimators for $h = 1$ and $h = 1/10$ using centered finite differences for the Split Coupling with $n = 10,000$ paths and not seeing any difference in the estimated values for the sensitivity (plots not shown). We then chose $h = 1/10$ to be conservative. Note that such a trial and error approach is often necessary when using finite difference methods as one does not *a priori* know the bias. This extra computational cost should be taken into account when deciding between finite difference methods and unbiased methods such as the Girsanov method.

See Figure 4 for the variances of the different methods when estimating $\frac{d}{d\kappa_2}\mathbb{E}[\text{Total dimers}]$. We note that, as expected, the simple act of sharing the compartment model provides the lion share of the variance reduction. We also note that the Split Coupling provides an estimator with such a low variance that it is difficult to differentiate from the x -axis. We therefore zoom in and provide in Figure 5 a plot of the three methods with the lowest estimator variance. In each, the compartment model is shared between the coupled processes (as detailed in Algorithm 3). The chemical models are coupled in the following ways: Common Random Variables (CRV), local Common Reaction Path (local-CRP), and the Split Coupling. As predicted by the work in Ref. 33, and as seen in the previous example, the local-CRP method and the Split Coupling method provide nearly identical variances. Finally, in Table II, we provide the simulation times and random variables required for the

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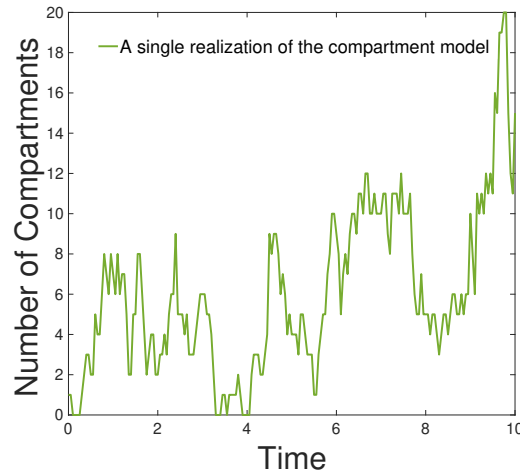


FIG. 3. A realization of the compartment model for the birth and death process of Example 3.

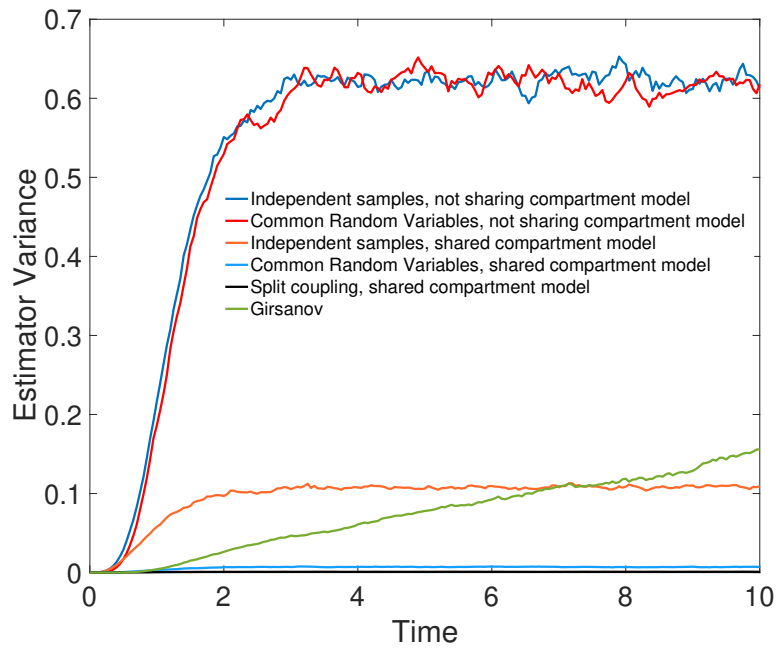


FIG. 4. Estimator variances (8) for $\frac{d}{d\kappa_2}\mathbb{E}[\text{Total dimers}]$ using various methods. For the (centered) finite difference methods, we used a perturbation of $h = 1/10$ and $n = 10,000$ coupled paths. For the Girsanov method we used $n = 20,000$ paths. We leave out the local-CRP method since it is indistinguishable from the Split Coupling and the x -axis.

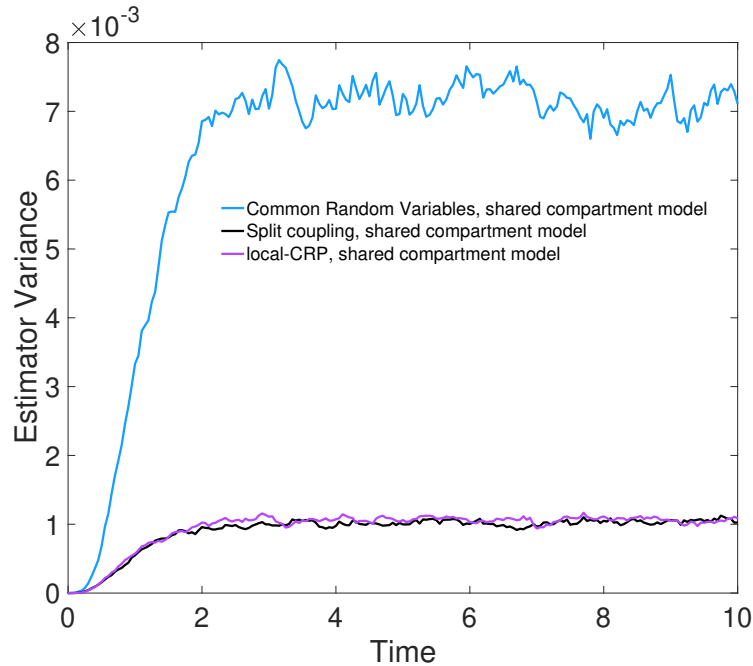


FIG. 5. Estimator variance (8) for $\frac{d}{d\kappa_2}\mathbb{E}[\text{Total dimers}]$ using various methods. Each method shares the compartment model. However, the chemical models are coupled in various ways including: Common Random Variables, local-CRP, and the Split Coupling. Note that this figure simply zooms in on the plots for Common Random Variables and the Split Coupling from Figure 4, while adding the plot for the local-CRP method.

various methods. As in the previous example, the Split Coupling, with shared compartments, is the most efficient. The relative slowness of the local-CRP method could possibly be alleviated via a different implementation in a different programming language, but it will presumably never be more efficient than the split coupling for this particular problem.

Estimation of $\frac{d}{d\kappa_F}\mathbb{E}[\text{Total dimers}]$. After using the same selection process for the perturbation, we once again chose a perturbation that is 10% of the nominal value: $h = 3/10$. We also again simulated $n = 10,000$ paths of the coupled processes and 20,000 paths for the Girsanov method. Figure 6 provides plots of the estimator variance for each method. The simulation times and numbers of random variables used are similar to those found in Table II, so we omit them. We note that up through time 2, the Girsanov method has a lower variance than the split coupling method. However, the variance of the Girsanov method increases monotonically as time increases and quickly becomes significantly higher than the

Method	Time	RVs used
Girsanov	308 seconds	1.5×10^9
Independent samples, not sharing compartment model	302 seconds	1.50×10^9
Common Random Variables, not sharing compartment model	322 seconds	1.50×10^9
Independent samples, shared compartment model	300 seconds	1.47×10^9
Common Random Variables, shared compartment model	368 seconds	1.48×10^9
local-CRP, shared compartment model	697 seconds	1.54×10^9
Split Coupling, shared compartment model	298 seconds	7.57×10^8

TABLE II. Simulation times for the various methods for the estimation of $\frac{d}{d\kappa_2}\mathbb{E}[\text{Total dimers}]$. $n = 10,000$ coupled paths were used for the finite difference methods and $n = 20,000$ paths were used for the Girsanov method.

Split Coupling.

We also note that the classical CRP method provides a variance that appears to be growing. This behavior is in line with the observations made in Ref. 26, where it was observed that the processes generated via the classical CRP method decouple as time increases, in which case the variance of the classical CRP method should approach that of independent samples.

The many parameter setting. Thus far, we have assumed that θ is one-dimensional. Consider now the case that $\theta \in \mathbb{R}^K$. In this case, our implementations would call for $K + 1$ path generations when we use a CRP method (either the local or classical), including the nominal process and each of the perturbed processes. However, the Split Coupling would require the generation of $2K$ paths (since we need a nominal process for each perturbation). If K is large, the CRP methods will overtake the Split Coupling in terms of efficiency.

To explore this, we consider again the mRNA-protein-dimer model, except now simultaneously perturb all $K = 6$ of the chemistry parameters. Because we are only perturbing the chemical parameters, we utilize the local-CRP coupling. We still use $n = 10,000$ paths for each method and simulate to a final time of 10. Also, for each parameter, we perturb by 10% of the nominal value (this choice does not affect simulation times or numbers of random variables used, which is our interest here). Our findings are summarized below.

- The local-CRP method took 4,401 seconds and required 5.31×10^9 random variables.

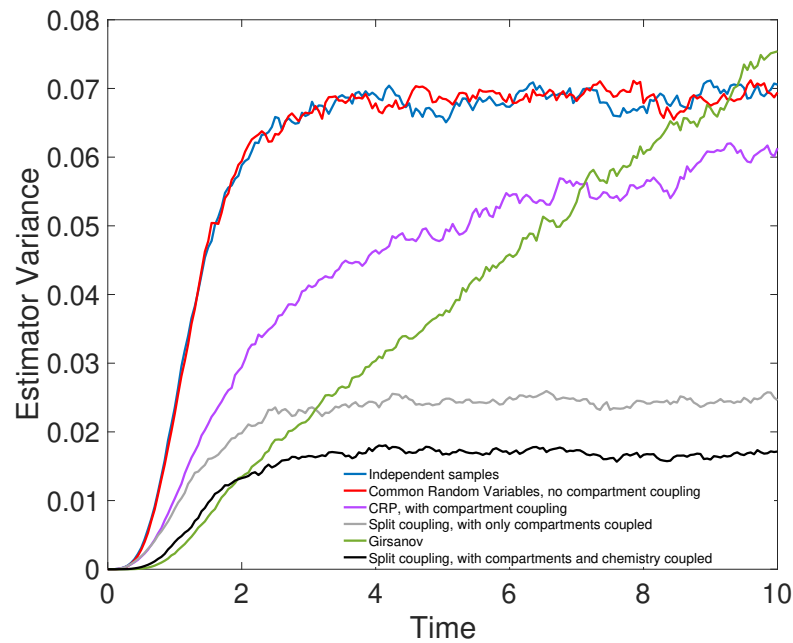


FIG. 6. Estimator variance (8) for $\frac{d}{d\kappa_F}\mathbb{E}[\text{Total dimers}]$ using various methods. For the (centered) finite difference methods, we used a perturbation of $h = 3/10$ and $n = 10,000$ paths. For the Girsanov method we used $n = 20,000$ paths.

These numbers are 6.3 and 3.45 times the values found when only a single parameter is perturbed (as reported in Table II). Note that $\frac{6+1}{2} = 3.5$ was the crude estimate for the factor of the increase in computational complexity.

- The Split Coupling method took 2,635 seconds and required 4.52×10^9 random variables. These numbers are 8.8 and 5.97 times the values found when only a single parameter is perturbed (as reported in Table II). Note that $\frac{2*6}{2} = 6$ was the crude estimate for the factor of the increase in computational complexity.

Taken together, we see that as the number of parameters being perturbed increases, the CRP method does, in fact, gain in efficiency as compared to the Split Coupling. When K is extremely large (with the specifics depending upon the problem at hand) the CRP methods, and the local-CRP method in particular, will become the most efficient. \square

V. DISCUSSION

In this paper, we have provided numerous methods utilizing Monte Carlo for parametric sensitivity analysis for RNIC models, as introduced in Ref. 21 and 22. In particular, we have synthesized work related to finite difference and Girsanov transform methods for parameteric sensitivity analysis for stochastic reaction networks and succinctly developed each of the relevant methods for this new, and more complex, modeling choice.

In terms of guidance, it seems clear that when only a small number of parameters is being perturbed, the Split Coupling is the most efficient studied here. However, as the number of parameters being perturbed increases, the CRP methods (and especially the local-CRP in cases when the parameters are from the chemical model) becomes the most efficient. When the shift happens (between the Split Coupling and the CRP methods) will be problem specific.

There are multiple avenues for future work. First, the RNIC model introduced here is the most “basic” version of the model, however it can be generalized in a number of ways. For example, it is possible to allow the transition rates of the compartment model (e.g., the fragmentation rate) to depend upon the contents of the compartments^{21,48}. It is not a priori obvious how to extend each of the developed methods to this different model in the most efficient manner possible. However, we hope that the extensions provided here, for the basic RNIC model, serve as a strong starting point.

Second, there are myriad other methods that have been developed for the estimation of parametric sensitivities for stochastic reaction networks that have not been extended to the RNIC framework within this paper. For example, we have not attempted to extend the Auxiliary Path Algorithm,³⁵ the Poisson Path Algorithm,³⁶ the hybrid pathwise approach,³¹ the Integral Path Algorithm³⁷, or the centered Girsanov transformation method⁴³, each of which is unbiased. We feel that each of these methods falls outside the scope of the current work, which largely focused on the development of coupling methods. It is possible that extensions of any of these methods could prove beneficial.

Third, we have not attempted to extend methods, such as that found in Ref. 49, for the estimation of second derivatives. Extending such methods is certainly worthy of consideration.

Finally, there is a significant amount of analysis that could be carried out to better

understand the finite difference methods introduced here. Unbiased Monte Carlo estimators, such as the Girsanov method, will converge to the true value of the quantity being estimated, in the sense of confidence intervals (or \mathcal{L}_2 error—i.e., accounting for both bias and estimator standard deviation) at a rate of $O(n^{-1/2})$, as $n \rightarrow \infty$, where n is the number of sample paths. For the centered finite difference methods, which have a bias that must be taken into account, determining the \mathcal{L}_2 convergence rate is more difficult. In the setting of reactions networks, the convergence rates can be $O(n^{-1/3})$ or $O(n^{-2/5})$, or something else, depending upon how $\text{Var}(f(X^{\theta+h/2}(t)) - f(X^{\theta-h/2}(t)))$ scales, as $h \rightarrow 0$. See section 2.1 of Ref. 26 for a detailed discussion of this topic. Determining how $\text{Var}(f(X^{\theta+h/2}(t)) - f(X^{\theta-h/2}(t)))$ scales, as $h \rightarrow 0$, for different finite difference methods in the case where X is an RNIC model would be a valuable piece of future work that could more rigorously determine when various methods should be used. Additionally, it is important to investigate how this scaling depends on the properties of the function f and the specific characteristics of the process X .

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Appendix A: Monte Carlo and finite difference methods for parametric sensitivities

The basic theory of Monte Carlo and finite difference methods for parametric sensitivities can be found in various papers and textbooks. No originality for this material is claimed.

Let $X^\theta : \mathbb{R}_{\geq 0} \rightarrow \mathbb{X}$ be a family, parameterized by $\theta \in \mathbb{R}$, of continuous-time stochastic processes with state space \mathbb{X} . In the setting of the current paper, X^θ is a continuous-time Markov chain with a discrete state space. We are assuming θ is one-dimensional here, but everything extends in the obvious manner if $\theta \in \mathbb{R}^K$ for some finite, positive integer K .

Let $f : \mathbb{X} \rightarrow \mathbb{R}$ be a function of the state of the system that gives a measurement of interest and define

$$J(\theta) := \mathbb{E} [f(X^\theta(t))].$$

The problem of interest is to efficiently estimate $\frac{d}{d\theta} J(\theta) = J'(\theta)$, and to do so using finite

difference methods with Monte Carlo. (The other method utilized in this paper, a Girsanov or Likelihood Transformation method, is discussed in Section III A.)

In order to estimate $J'(\theta)$, it is natural to utilize a centered finite difference:

$$J'(\theta) \approx \frac{\mathbb{E} [f(X^{\theta+h/2}(t))] - \mathbb{E} [f(X^{\theta-h/2}(t))]}{h}, \quad (\text{A1})$$

as its bias is $O(h^2)$, as $h \rightarrow 0$, see Ref. 23. This should be compared with the forward difference, which has a bias of $O(h)$

$$J'(\theta) = \frac{\mathbb{E} [f(X^{\theta+h}(t))] - \mathbb{E} [f(X^{\theta}(t))]}{h} + O(h).$$

The estimator for (A1) using centered finite differences is

$$D_n(h) = \frac{1}{n} \sum_{\ell=1}^n d_{[\ell]}(h), \quad (\text{A2})$$

with

$$d_{[\ell]}(h) = \frac{f(X_{[\ell]}^{\theta+h/2}(t)) - f(X_{[\ell]}^{\theta-h/2}(t))}{h}, \quad (\text{A3})$$

where $X_{[\ell]}^{\theta}$ represents the ℓ th path generated with parameter choice θ , n is the number of paths generated, and the $d_{[\ell]}(h)$ are generated independently.

Many computations are performed with a target variance (which yields a target size of the confidence interval). Denoting the target variance by V^* , we see that the number of paths required is approximated by the solution to

$$\text{Var} \left(\frac{1}{n} \sum_{\ell=1}^n d_{[\ell]}(h) \right) = \frac{1}{n} \text{Var}(d(h)) = V^* \implies n = \frac{1}{V^*} \text{Var}(d(h)).$$

Thus, decreasing the variance of $d(h)$ lowers the computational complexity (total number of computations) required to solve the problem.

The basic idea of coupling is to lower the variance of $d(h)$ by simulating $X^{\theta+h/2}$ and $X^{\theta-h/2}$ simultaneously, i.e., generating them on the same probability space, so that the two processes are highly correlated or “coupled.” That is, instead of generating paths independently, we want to generate a pair of paths $(X^{\theta+h/2}, X^{\theta-h/2})$ so that the variance of $f(X^{\theta+h/2}(t)) - f(X^{\theta-h/2}(t))$ is reduced. The basic idea of any such coupling is to reuse, or share, some portion of randomness in the generation of each process. The couplings utilized in this paper, found in Section III, include using Common Random Variables (i.e., simply reusing the seed of the random number generator before generating each path), versions of

the Common Reaction Path method³² and local-Common Reaction Path method,³³ and a version of the Split Coupling.²⁶

That all said, it is not enough to simply provide a low variance estimator without taking the bias of the method into account. Thinking in terms of confidence intervals, it is clear that there is little reason to desire a standard deviation for an estimator that is significantly less than its bias. This idea can be made precise by considering the \mathcal{L}_2 error of an estimator. For example, if we denote the bias of our estimator (A2) by $B(h) = |J'(\theta) - \mathbb{E}[D_n(h)]|$, then the square of the \mathcal{L}_2 error is

$$\mathbb{E} [|J'(\theta) - D_n(h)|^2] = \mathbb{E} [|J'(\theta) - \mathbb{E}[D_n(h)] + \mathbb{E}[D_n(h)] - D_n(h)|^2] = B(h)^2 + \text{Var}(D_n(h)).$$

Moreover, as noted above, as $h \rightarrow 0$ the bias shrinks for our finite difference methods but the variance tends to infinity (because of the division by h). Hence, there is a subtle bias-variance tradeoff that must be accounted for with these methods.

Appendix B: Standard algorithms for stochastic reaction networks

We provide the Gillespie algorithm^{12,13} and the next reaction method^{40,41}, which are the two exact simulation methods that are most widely used. We also provide a Gillespie version of the Girsanov transformation method.

We remind that throughout this work, we assume a reaction network with reaction vectors denoted by $\zeta_k \in \mathbb{Z}^d$ and intensity functions (or rate functions) denoted by λ_k , where we have indexed the reactions by k . For the sake of clarity, we will denote (in this section only) the number of reaction types by R .

We first provide Gillespie's algorithm^{12,13}.

Algorithm 4 (Gillespie's algorithm). *Given: a reaction network with reaction vectors $\{\zeta_k\}_{k=1}^R$ and intensity functions $\{\lambda_k\}_{k=1}^R$, an initial distribution, μ , on $\mathbb{Z}_{\geq 0}^d$.*

Repeat steps 3 – 8 until a stopping criteria is reached. All calls to random variables are independent from all others.

1. Determine $X(0)$ via μ .
2. Set $t = 0$.
3. For each $k \in \{1, \dots, R\}$, determine $\lambda_k(X(t))$ and set $\lambda_{tot} = \sum_{k=1}^R \lambda_k(X(t))$.

4. Let u_1, u_2 be independent random variables that are uniformly distributed on $[0, 1]$.
5. Set $\Delta = -\ln(u_1)/\lambda_{tot}$.
6. Find $\ell \in \{1, \dots, R\}$ so that

$$\frac{1}{\lambda_{tot}} \sum_{k=1}^{\ell-1} \lambda_k(X(t)) \leq u_2 < \frac{1}{\lambda_{tot}} \sum_{k=1}^{\ell} \lambda_k(X(t)).$$

7. Set $X(t + \Delta) = X(t) + \zeta_\ell$.
8. Set $t \leftarrow t + \Delta$.

We now provide the next reaction method, as it appeared in Ref. 40. Note that this algorithm is simply a method for simulating Kurtz's representation (1). Essentially the same algorithm (though with the addition of the usage of index priority queues) appeared in Ref. 41.

Algorithm 5 (Next Reaction method⁴⁰). *Given: a reaction network with reaction vectors $\{\zeta_k\}_{k=1}^R$ and intensity functions $\{\lambda_k\}_{k=1}^R$, an initial distribution, μ , on $\mathbb{Z}_{\geq 0}^d$.*

Repeat steps 5 – 10 until a stopping criteria is reached. All calls to random variables are independent from all others.

1. Determine $X(0)$ via μ .
2. Set $t = 0$.
3. For each $k \in \{1, \dots, R\}$, set $T_k = 0$.
4. Let $\{e_k\}_{k=1}^R$ be a collection of independent unit-exponential random variables and for each $k \in \{1, \dots, R\}$, set $P_k = e_k$.
5. For each $k \in \{1, \dots, R\}$, determine $\lambda_k(X(t))$.
6. Find the minimum of the values $\left\{ \frac{P_k - T_k}{\lambda_k(X(t))} \right\}_{k=1}^R$. Denote the minimum by Δ and denote the index of the minimum value by ℓ .
7. Set $X(t + \Delta) = X(t) + \zeta_\ell$.
8. For each $k \in \{1, \dots, R\}$, set $T_k = \lambda_k(X(t)) \cdot \Delta$.
9. Set $P_\ell \leftarrow P_\ell + e_0$, where e_0 is a unit-exponential random variable (independent from previous).

10. Set $t \leftarrow t + \Delta$.

We turn to the Girsanov transformation method, often called the Likelihood Transformation method outside of the biosciences. See either Ref. 25 or Ref. 23 for relevant references. For concreteness, we will assume stochastic mass-action kinetics and we suppose that we are computing the derivative of $\mathbb{E}[f(X(t_{\text{end}}))]$ with respect to the rate parameter κ_j , where t_{end} is some fixed time. We will denote the required weight function by $W(t)$. Therefore, the output of the algorithm consists of both $X(t_{\text{end}})$ and $W(t_{\text{end}})$, which can be used as an unbiased estimator $\frac{\partial}{\partial \kappa_j} \mathbb{E}[f(X(t_{\text{end}}))] \approx \frac{1}{n} \sum_{\ell=1}^n f(X_{[\ell]}(t_{\text{end}})) \cdot W_{[\ell]}(t_{\text{end}})$, where the subscript $[\ell]$ enumerates the independent realizations.

Algorithm 6 (Girsanov transformation method). *Given: a reaction network with reaction vectors $\{\zeta_k\}_{k=1}^R$ and intensity functions $\{\lambda_k\}_{k=1}^R$, an initial distribution, μ , on $\mathbb{Z}_{\geq 0}^d$.*

All calls to random variables are independent from all others.

1. Determine $X(0)$ via μ .
2. Set $t = 0$ and $W(0) = 0$.
3. For each $k \in \{1, \dots, R\}$, determine $\lambda_k(X(t))$ and set $\lambda_{\text{tot}} = \sum_{k=1}^R \lambda_k(X(t))$.
4. Let u_1, u_2 be independent random variables that are uniformly distributed on $[0, 1]$.
5. Set $\Delta = -\ln(u_1)/\lambda_{\text{tot}}$.
6. If $t + \Delta > t_{\text{end}}$, do the following (otherwise, proceed to step 7):
 - (a) set $W(t_{\text{end}}) = W(t) - (t_{\text{end}} - t) \cdot \frac{\lambda_j(X(t))}{\kappa_j}$,
 - (b) set $X(t_{\text{end}}) = X(t)$,
 - (c) break from the algorithm and report $X(t_{\text{end}})$ and $W(t_{\text{end}})$.

7. Find $\ell \in \{1, \dots, R\}$ so that

$$\frac{1}{\lambda_{\text{tot}}} \sum_{k=1}^{\ell-1} \lambda_k(X(t)) \leq u_2 < \frac{1}{\lambda_{\text{tot}}} \sum_{k=1}^{\ell} \lambda_k(X(t)).$$

8. If $\ell = j$, set

$$W(t + \Delta) = W(t) + \frac{1}{\kappa_j} - \frac{\lambda_j(X(t))}{\kappa_j} \cdot \Delta$$

otherwise, if $\ell \neq j$, set

$$W(t + \Delta) = W(t) - \frac{\lambda_j(X(t))}{\kappa_j} \cdot \Delta.$$

9. Set $X(t + \Delta) = X(t) + \zeta_\ell$.

10. Set $t \leftarrow t + \Delta$, and return to step 3.

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