

A confidence-based method for selecting species criticality in  $\tau$ -leaping

**Look before you leap: A confidence-based method for selecting species criticality whilst avoiding negative populations in  $\tau$ -leaping**

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(Dated: 21 January 2011)

The stochastic simulation algorithm was introduced by Gillespie and in a different form by Kurtz. There have been many attempts at accelerating the algorithm without deviating from the behavior of the simulated system. The crux of the explicit  $\tau$ -leaping procedure is the use of Poisson random variables to approximate the number of occurrences of each type of reaction event during a carefully selected time period,  $\tau$ . This method is acceptable providing the leap condition, that no propensity function changes “significantly” during any time-step, is met. Using this method there is a possibility that species numbers can, artificially, become negative. Several recent papers have demonstrated methods that avoid this situation. One such method classifies, as critical, those reactions in danger of sending species populations negative. At most one of these critical reactions is allowed to occur in the next time-step.

We argue that the criticality of a reactant species and its dependent reaction channels should be related to the probability of the species number becoming negative. This way only reactions that, if fired, produce a high probability of driving a reactant population negative are labeled critical. The number of firings of more reaction channels can be approximated using Poisson random variables thus speeding up the simulation whilst maintaining accuracy. In implementing this revised method of criticality selection we make use of the probability distribution from which the random variable describing the change in species number is drawn. We give several numerical examples to demonstrate the effectiveness of our new method.

PACS numbers: 82.20.Uv,05.40.-a,82.20.Sb,82.20.Wt,02.50.Cw,  
82.20.Wt,82.20.Db,82.30.-b

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## I. INTRODUCTION

Many biological processes are inherently stochastic and, in recent years, the modeling of such mechanisms has become a particularly important field. These stochastic processes take place over widely varying spatial scales, from interactions between organisms<sup>23</sup> on the macro-scale through to cell migration<sup>3</sup> on the meso-scale right down to gene regulatory networks<sup>9</sup> on the micro-scale, with a myriad of other sub-cellular and super-cellular processes in between<sup>2</sup>. These systems are modeled through a series of interactions, be they locusts sensing each other and reacting to each others' movements, cells migrating from one area of a domain to another or molecules reacting with each other. For consistency throughout the rest of this paper, we will use the terminology of a chemical system, referring to these interactions as 'reactions' and to interacting groups as 'species', although the algorithms outlined here could equally well be applied to systems that do not represent chemical reactions. In many cases the 'reactive collisions' associated with these 'chemical species' can be modeled using the stochastic simulation algorithm (SSA).

Introduced by Gillespie<sup>10,11</sup> (and in a different form by Kurtz<sup>20</sup>), the stochastic simulation algorithm (SSA) can be used to simulate a well-stirred system of  $N \geq 1$  chemical species,  $\{S_1, \dots, S_N\}$ , interacting stochastically through  $M$  reaction channels  $\{R_1, \dots, R_M\}$ . We denote the state of the system at time  $t$  by the vector  $\mathbf{X}(t) = (X_1(t), \dots, X_N(t))$ , where  $X_i(t)$  represents the number of molecules of  $S_i$  at time  $t$ . We aim to simulate the evolution of  $\mathbf{X}(t)$  given some initial condition  $\mathbf{X}(t_0) = \mathbf{x}_0$ . The dynamics of each reaction channel,  $R_j$ , (for  $j = 1, \dots, M$ ) are completely characterized by a propensity function,  $a_j(\mathbf{x})$ , and a stoichiometric vector,  $\boldsymbol{\nu}_j = (\nu_{1j}, \dots, \nu_{Nj})$ . The propensity functions are such that  $a_j(\mathbf{x})dt$  defines the probability that, given  $\mathbf{X}(t) = \mathbf{x}$ , one  $R_j$  reaction will 'fire' during the next infinitesimal time interval,  $dt$ .  $\nu_{ij}$  represents the change in the population of  $S_i$  caused by one 'firing' of the  $R_j$  reaction channel. For each reaction channel,  $R_j$ , the state change vector,  $\boldsymbol{\nu}_j$ , is defined once at the beginning of simulation but the propensity functions will usually change dynamically with the state vector,  $\mathbf{X}(t)$ , and thus require updates at each time-step.

One implementation of this mathematically exact procedure for simulating the

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progression of a system is known as the direct method<sup>11</sup>. Given a system at time  $t$  in state  $\mathbf{X}(t)$ , a time interval  $\tau$ , until the next reaction occurs, is generated. Along with it a reaction, with index  $j$ , is chosen to occur at time  $t + \tau$ . The changes in the numbers of molecules caused by the firing of reaction channel  $R_j$  are implemented, the propensity functions are altered accordingly and the time is updated, ready for the next  $(\tau, j)$  pair to be selected. A method for the implementation of this algorithm is given by Gillespie<sup>11</sup>.

The SSA records the exact history of a system, stepping between individual reaction events in the finest detail. This approach is simultaneously the Herculean strength and the Achilles' heel of the SSA. The construction of every reaction event gives a complete history of  $\mathbf{X}(t)$ , but considering every reaction is time consuming and computationally expensive.

If some losses in accuracy are acceptable then a faster, but approximate, method, the explicit  $\tau$ -leaping algorithm<sup>12</sup>, is available. Instead of stepping gingerly between individual reactions, the accelerated method leaps temeritously through time, allowing several reaction events from each channel to occur between updates of the state vector. This accelerated method is not, however, completely reckless as it is constrained by the so-called 'leap condition'<sup>12</sup>. This states that all leaps should be sufficiently small that the change in the state vector will be so slight that no propensity functions have their values changed "significantly" during a leap. The number of firings,  $k_j$ , of each reaction channel,  $R_j$ , during a leap can be approximated using samples of the Poisson random variable,  $\mathcal{P}(a_j(\mathbf{x})\tau)$ , for sufficiently small  $\tau$ . This provides us with a formula by which to update the state vector,

$$\mathbf{X}(t + \tau) = \mathbf{x} + \sum_{j=1}^M \boldsymbol{\nu}_j \mathcal{P}(a_j(\mathbf{x})\tau). \quad (1)$$

The accuracy of this approximation depends on the extent to which the leap condition is observed. If propensity functions change appreciably during the leap then we will be simulating reactions from the wrong Poisson distribution. What exactly constitutes an appreciable change in a propensity function and consequently how to choose  $\tau$  is the subject of much debate<sup>1,6,12,13</sup>. The original<sup>12</sup> method bounds

the change in each propensity function by  $\varepsilon a_0(\mathbf{x})$ , where  $0 < \varepsilon \ll 1$  is known as the error control parameter. Throughout the rest of this paper and in all numerical simulations we fix  $\varepsilon = 0.03$ , a canonical value used by Cao et al.<sup>5,6</sup>. This bound on the change in propensity function gives a method of bounding  $\tau$  and completes the description of the basic explicit  $\tau$ -leaping algorithm (see Cao et al.<sup>6</sup>, Gillespie<sup>12</sup>).

Since the Poisson random variable can have arbitrarily large sample values, it is possible that a reaction channel may fire so many times that it will deplete one or more of its reactants by a larger number than are actually available. One method of preventing this unphysical behavior, presented by Tian and Burrage<sup>22</sup> and independently by Chatterjee et al.<sup>8</sup> is known as Binomial  $\tau$ -leaping. This relies on approximating the number of firings,  $k_j$ , of a reaction channel,  $R_j$ , by a sample from a Binomial distribution whose values are naturally bounded. Due to the poor correspondence between the Poisson and Binomial distributions in the case of small species numbers,  $x_i$ , (the case with which we will most often be concerned when attempting to avoid negative populations) and over-cautious restrictions on the number of reactions that can fire, the Binomial  $\tau$ -leap method tends to be less accurate than the SSA and the more recent ‘modified Poisson  $\tau$ -leaping’ procedure<sup>5</sup>, both of which circumvent the problem of negative species.

The modified Poisson  $\tau$ -leaping procedure relies on identifying reactions that, if fired more than a predefined ‘critical’ number of times, will cause one or more of their contingent species populations to become negative. The number of ‘allowed’ firings of a reaction,  $R_j$ , will be denoted by  $L_j$ . Reactions are partitioned into critical and non-critical subsets with, at most, one of the critical reactions being able to fire per leap, by a process akin to the exact SSA. This ensures the reactant species depleted by the critical reaction do not become negative. The more critical reactions we have the slower the simulation becomes. Defining critical reactions should, therefore, be an important part of any algorithm. However, the size of the critical number of firings,  $n_c$ , is difficult to determine and Cao et al.<sup>5</sup>, suggest a value between 2 and 20.

Widely varying reaction rate constants can cause reaction channels to have very different propensity functions and hence probabilities of driving the species popu-

lation negative. Even when reactions have the same reaction rate constants, differing numbers of molecules undergoing the same reaction will have widely varying probabilities of becoming negative. If we choose  $n_c$  to be small then we run the unacceptable risk of ignoring reactions that have a high probability of their species populations becoming negative. However, choosing  $n_c$  to be too large risks classifying reactions, which have near-infinitesimal probabilities of becoming negative, as critical, slowing the simulation. Including rates of reaction that may vary over orders of magnitude and the fact that species numbers may be re-populated during a reaction complicates matters still further. A method for deciding the criticality of a reaction based on the *probability* of any one of its *contingent species* becoming negative would be preferable.

Using estimations of the current propensity functions, we derive the precise probability distribution for  $\Delta_\tau X_i$ , which describes the change in reactant species  $i$ , as the sums and/or differences of Poisson  $m$ -lets<sup>16</sup>. Using this distribution we choose a confidence level and determine whether the probability (that the sample drawn from the random variable will be larger than the number of reactants remaining) falls outside this interval. Species for which the probability of becoming negative is high enough to fall outside the confidence interval will be marked as critical as will the reactions that depend upon them. This method will give us much more controlled consistency when deciding reaction criticality. The speed of the algorithm should be increased as we will no longer mark reactions that do not have a significant probability of driving one of their contingent species negative as critical.

The remainder of this paper will be structured as follows: In section II we briefly outline the modified  $\tau$ -leaping procedure of Cao et al.<sup>5</sup>, which is the current gold standard for avoiding negative populations. We also explicitly describe the method of Cao et al.<sup>6</sup> for efficient step size selection. In Section III we introduce a revised method which increases confidence in our choice of reaction criticality. Numerical simulations that demonstrate the improved efficiency and accuracy of our method of criticality selection will be performed in Section IV and the implications of our adapted techniques will be discussed in Section V.

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## II. BACKGROUND

### A. Some useful results from binomial $\tau$ -leaping

We have already informally introduced  $L_j$  as the number of firings of a reaction,  $R_j$ , before it sends one of its contingent species negative, providing no new molecules of that reactant species are created. More formally this has been expressed as<sup>5,6</sup>

$$L_j = \min_{i=1, \dots, N; \nu_{ij} < 0} \left\lceil \frac{x_i}{-\nu_{ij}} \right\rceil, \quad (2)$$

where  $\lceil x \rceil$  represents the smallest integer in  $x$ .

Tian and Burrage<sup>22</sup> introduce Property 1:

*Property 1: If  $\mathcal{P}_1 = \mathcal{P}(\lambda_1)$  and  $\mathcal{P}_2 = \mathcal{P}(\lambda_2)$  are two independent Poisson random variables with means  $\lambda_1$  and  $\lambda_2$ , respectively, then  $\mathcal{P}_1 + \mathcal{P}_2$  is also a Poisson,  $\mathcal{P}(\lambda_1 + \lambda_2)$ , with mean  $\lambda_1 + \lambda_2$ .*

This property can be found in any basic text on univariate discrete distributions, Johnson et al.<sup>16</sup> for example. We also introduce two new properties employed in section III.

*Property 2: If  $\mathcal{P}_1 = \mathcal{P}(\lambda_1)$  and  $\mathcal{P}_2 = \mathcal{P}(\lambda_2)$  are two independent Poisson random variables with means  $\lambda_1$  and  $\lambda_2$  respectively, then their difference  $\mathcal{P}_1 - \mathcal{P}_2$  is given by a Skellam distribution, with mean  $\lambda_1 - \lambda_2$  and variance  $\lambda_1 + \lambda_2$ . The probability mass function (PMF) of the Skellam distribution takes the form*

$$\text{Pr}(k; \lambda_1, \lambda_2) = e^{-(\lambda_1 + \lambda_2)} \left( \frac{\lambda_1}{\lambda_2} \right)^{k/2} I_{|k|}(2\sqrt{\lambda_1 \lambda_2}), \quad (3)$$

where  $I_k(z)$  is the modified Bessel function of the first kind.

The proof of Property 2 is given in Appendix VI A. Using Property 1 recursively in combination with Property 2 we can also show that the sum and/or difference of arbitrarily many Poisson distributions is also Skellam distributed.

If  $\mathcal{P}^m$  is Poisson distributed but with support  $0, m, 2m, 3m \dots$ , for  $m \in \mathbb{Z}$ , instead of integer support, then we call it a Poisson  $m$ -let. i.e.  $m = 1$  gives the usual Poisson distribution or Poisson singlet,  $m = 2$  gives a Poisson doublet etc.

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*Property 3: If  $\mathcal{P}^m = m \times \mathcal{P}(\lambda_1)$  and  $\mathcal{P}^n = n \times \mathcal{P}(\lambda_2)$  are a Poisson  $m$ -let and a Poisson  $n$ -let respectively, where  $m, n \in \mathbb{Z}$  then their sum  $\mathcal{P} = \mathcal{P}^m + \mathcal{P}^n$  is distributed as a Poisson stopped sum distribution.*

The proof of Property 3 is given in Appendix VI B. Since in the statement of Property 3 we assume  $m, n \in \mathbb{Z}$  the formulae apply equally well to negative values of  $m$  and  $n$  as to positive values and hence, to differences as well as sums of Poisson  $m$ -lets. It is also a trivial extension to prove that the sum or difference of Poisson stopped sum distributions is also a Poisson stopped sum distribution. From the individual Poisson  $m$ -lets we can find the probability generating function (PGF) of the Poisson stopped sum distribution and from the PGF we can find the PMF and hence the cumulative mass function (CMF).

## B. Modified Poisson $\tau$ -leaping

It is possible, in the original formulation of the  $\tau$ -leaping algorithm, that the Poisson approximation to  $k_j$  in equation (1) might result in so many firings of a reaction,  $R_j$ , that the population of a contingent species becomes negative.

The modified Poisson  $\tau$ -leaping algorithm<sup>5</sup> arose from the observation that, typically, negative populations are caused by multiple firings of reactions that are only a few firings away from exhausting the numbers of one or more of their reactants. The algorithm introduces a second control parameter,  $n_c$ , a positive integer, usually set between 2 and 20, such that any reaction within  $n_c$  firings of exhausting one of its contingent species is classified as critical. We denote this method of criticality-selection as the CGP method. This method selects  $\tau$  so that, at most, one firing occurs between all the critical reactions, using an adapted version of the SSA. This restriction means that negative populations are almost completely avoided. However, because Poisson random variables are still being used there is still a small possibility (due to the non-critical reactions) of negative species populations occurring. On these rare occasions a leap can simply be rejected and repeated with a reduced  $\tau$ <sup>5</sup>. An algorithm for the modified  $\tau$ -leaping method is given in Cao et al.<sup>5</sup>.



### C. CGP method for $\tau$ -selection

The CGP  $\tau$ -selection procedure attempts to choose  $\tau$  so that leaps are as large as possible. It is also less computationally intensive than previous methods<sup>5,12</sup>. This, in combination with larger leap sizes, causes simulation speeds to increase. The CGP method’s key idea is to bound the *relative* change in *species numbers* explicitly. By bounding the expected change in species numbers the method implicitly bounds the expected change in propensity functions in such a manner that the leap condition is still approximately preserved.

In the  $\tau$ -selection method of Gillespie<sup>12</sup> the leap condition is realized by bounding the absolute value of the change in each propensity function,  $\Delta_\tau a_j(\mathbf{x})$ , in time-step,  $\tau$ , by a small fraction,  $\varepsilon$ , of the sum of the propensity functions,  $a_0(\mathbf{x})$ . This does not limit the changes of the propensity functions in a particularly uniform manner<sup>6</sup>. The aim of the leap condition is to ensure that every propensity function remains practically constant during a leap. This can be achieved more consistently if we bound the relative changes in propensity functions as follows

$$|\Delta_\tau a_j(\mathbf{x})| \leq \max\{\varepsilon a_j(\mathbf{x}), c_j\}, \quad j = 1, \dots, M, \quad (4)$$

where  $c_j$  is the minimum amount by which the propensity function  $a_j(\mathbf{x})$ , for reaction  $R_j$ , can change. This second argument of the maximization eliminates the probability of  $\tau$  tending to zero as the size of a single propensity function tends to zero<sup>6</sup>.

The relative changes in the propensity functions can be bounded approximately by bounding the relative changes in their corresponding reactions’ contingent species. Instead of choosing  $\tau$  using condition (4) we can use

$$|\Delta_\tau X_i| \leq \max\{\varepsilon_i x_i, 1\}. \quad (5)$$

Here the second argument of the maximization (in analogy to condition (4)), the smallest amount by which a species number can change, is used to avoid  $\tau$  approaching zero. For each reactant species,  $S_i$ , we find the highest order reaction in which  $S_i$

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is a reactant and choose  $\varepsilon_i$  appropriately according to the rules given in Cao et al.<sup>6</sup>. Considering a rearrangement of equation (1):

$$\Delta_\tau X_i = \sum_{j \in J_{ncr}} \nu_{ij} \mathcal{P}_j(a_j(\mathbf{x})\tau), \quad (6)$$

where  $J_{ncr}$  is the set of non-critical reactions, we can bound  $\Delta_\tau X_i$  according to condition (5) by choosing an appropriate value of  $\tau$ . The interpretation of equation (6) will determine how stringently the leap condition is adhered to.

The CGP  $\tau$ -selection method uses the mean and variance of the distribution of  $\Delta_\tau X_i$  given by equation (6) to place a bound on  $\tau$  as follows. The mean and variance can be calculated straightforwardly as

$$\langle \Delta_\tau X_i \rangle = \sum_{j \in J_{ncr}} \nu_{ij} a_j(\mathbf{x})\tau, \quad (7)$$

$$\text{var}\{\Delta_\tau X_i\} = \sum_{j \in J_{ncr}} \nu_{ij}^2 a_j(\mathbf{x})\tau. \quad (8)$$

The bound in equation (5) on  $|\Delta X_i|$  and hence the bound on the change in the propensity functions given by equation (4) may be considered ‘substantially satisfied’<sup>6,12,13</sup> if

$$|\langle \Delta_\tau X_i \rangle| \leq \max\{\varepsilon_i x_i, 1\}, \quad (9)$$

$$\sqrt{\text{var}\{\Delta_\tau X_i\}} \leq \max\{\varepsilon_i x_i, 1\}, \quad (10)$$

are simultaneously satisfied. Substituting equations (7) and (8) into the above bounds on  $\Delta_\tau X_i$  (equations (9) and (10) respectively) gives two separate bounds on  $\tau$ , both of which we require to be satisfied. Defining

$$\hat{\lambda}_i = \sum_{j \in J_{ncr}} \nu_{ij} a_j(\mathbf{x}), \quad (11)$$

$$\hat{\sigma}_i^2 = \sum_{j \in J_{ncr}} \nu_{ij}^2 a_j(\mathbf{x}), \quad (12)$$

for each reactant species,  $i$ . The CGP  $\tau$ -selection procedure for non-critical reactions

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is given by

$$\tau' = \min_{i \in I_{ncr}} \left\{ \frac{\max\{\varepsilon_i x_i, 1\}}{|\hat{\lambda}|}, \frac{\max\{\varepsilon_i x_i, 1\}^2}{\hat{\sigma}_i^2} \right\}, \quad (13)$$

where  $I_{ncr}$  is the set of non-critical species, i.e. those species which participate (either as reactants or products) in non-critical reactions,  $R_j$ , such that  $j \in J_{ncr}$ .

### III. INCORPORATING CONFIDENCE MEASURES FOR CRITICALITY SELECTION

Consider a simple degradation reaction,  $S_1 \xrightarrow{c_1} \phi$ . The expected number of firings for this reaction is  $\lambda = x_1 c_1 \tau$ . Taking an arbitrary value for the rate constant multiplied by the time-step, e.g.  $c_1 \tau = 0.1$  we find that the probability of species numbers becoming negative, when the number of firings of the reaction is drawn from a Poisson distribution with mean,  $\lambda$ , is drastically different depending on the number of molecules of the species,  $x_1$ . For example, if  $x_1 = 10$ , the probability of the species becoming negative is approximately  $10^{-8}$ . However, if  $x_1 = 2$ , the probability increases to  $10^{-3}$ , five orders of magnitude larger. Choosing the critical species number to be  $n_c = 1$ , our second example is not flagged as critical despite the high probability of the population becoming negative. Conversely choosing  $n_c$  to be larger, i.e.  $n_c = 10$ , then species which have very small probabilities of becoming negative are labeled as critical and their dependent reactions are restricted unnecessarily, slowing the simulation.

Even this simplified view presents problems for the CGP method of determining criticality. This example ignores the issues of differing reaction rates and the fact that reactant species may be re-populated during a leap, making it less likely for their population to become extinct. Different reactant species require levels of criticality dependent on their population size and on the rates of reactions that deplete and add to their numbers. The criticality of each reaction will depend on the criticality of its contingent species. This hints that taking a single critical value for all reactions is not appropriate.

If we are to draw a Poisson random number of firings of a reaction channel we would like to ensure that the probability that we take any of the contingent

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species' populations negative is less than some threshold value,  $P_c = \alpha/100$ , for example. This is the basis for a one-sided confidence interval. If the probability of the population becoming negative goes above  $P_c$  then we regard this reaction as critical. This way we eliminate reactions being unnecessarily labeled as critical when in fact they can undergo Poisson  $\tau$ -leaping with an infinitesimally small probability of sending the populations of their contingent reactant species negative.

In order to find the probability of a reactant species' population becoming negative we consider the distribution  $\Delta_\tau X_i$  of its change. A problem occurs in that the value of  $\tau$  is unknown and cannot be chosen until we have decided which reactions are critical and which are not. This 'chicken and egg' situation can be resolved by invoking the leap condition, which states that the propensities should not change significantly between steps. This implies their sum should not change too much and hence the size of the time-step should, on average, be approximately the same. We can, therefore, evaluate  $\Delta_\tau X_i$  using the value of the previous time-step,  $\tau$ . Consider the distribution (6) of the random variable  $\Delta_\tau X_i$ :

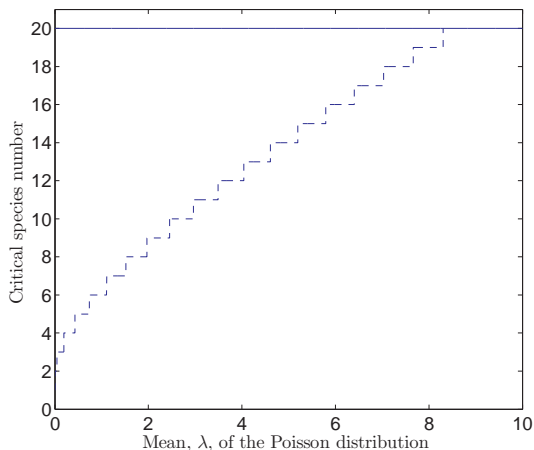
$$\Delta_\tau X_i = \sum_{j \in J_{ncr}} \nu_{ij} \mathcal{P}_j(a_j(\mathbf{x})\tau).$$

Property 3 states that the sum of Poisson  $m$ -lets is given by a Poisson stopped sum distribution. This is precisely the situation when considering the distribution of  $\Delta_\tau X_i$ , where  $m$  is replaced by  $\nu_{ij}$  and we assume, that the Poisson random variables,  $\mathcal{P}_j(a_j(\mathbf{x})\tau)$ , describing the number of firings of the reactions dependent on reactant  $S_i$ , are uncorrelated. The  $2q$  parameters (where  $q$  is the highest order of the reaction that reactant  $S_i$  is involved in) of the Poisson stopped sum distribution, given in equation (6), all depend linearly on  $\tau$ . Given a predefined confidence interval we can use the PMF of this distribution to calculate the CMF and hence to calculate a critical surface for species numbers, below which species will be defined as critical.

Figure 1 displays such a criticality surface for the simplest case  $\Delta_\tau X_i = -\sum \mathcal{P}_j(a_j(\mathbf{x})\tau)$ , where species  $i$  is depleted by linear reaction channels (i.e.  $\nu_{ij} = -1$ ). It also shows for comparison the effective criticality curve for the CGP method of  $\tau$ -selection, with  $n_c = 20$ . When simulating our revised method for values of the parameter that

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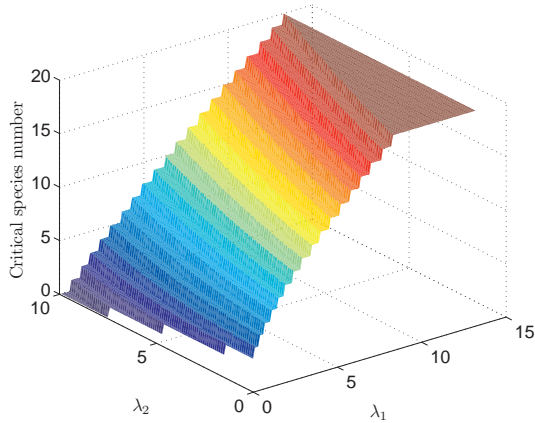
would give species criticality values above 20 we take the species criticality value to be exactly 20. This threshold is necessitated by the fact that we can not calculate the value of the species criticality curve for all possible (infinitely many) values of the parameter of the Poisson distribution. As such, we assign a maximum criticality threshold of 20 which, as the maximum value of  $n_c$  considered by Cao et al.<sup>5</sup>, has previously been shown to be robust in avoiding negative populations in  $\tau$ -leaping.



**FIG. 1:** An example critical curve for purely linear species depletions with criticality level  $\alpha = 0.001$ . The values on the  $x$ -axis represent the mean,  $\lambda$ , of the Poisson distribution depleting the species  $i$  and the dashed curve represents the value of  $x_i$  above which species  $i$  is not classified as critical. The full line represents the effective criticality curve of the CGP method ( $n_c = 20$ ).

In a more complicated scenario, in which a species undergoes linear degradation and creation reactions during each  $\tau$ -leap, the species is depleted by a Poisson distribution with mean  $\lambda_1$  but replenished by a Poisson distribution with mean  $\lambda_2$ . The random variable describing the number of molecules of the species that are depleted is drawn from a Skellam distribution with mean  $\lambda_1 - \lambda_2$  and variance  $\lambda_1 + \lambda_2$  given by  $-\Delta_\tau X_i = \mathcal{P}_1(\lambda_1) - \mathcal{P}_2(\lambda_2)$ . For the two parameters of this Skellam distribution,  $\lambda_1$  and  $\lambda_2$ , we can calculate a critical *surface*, below which species will be considered critical (see Fig. 2). This criticality surface is sufficient for all sets of linear reactions. Similar curves/surfaces can be calculated for non-linear reactions using the more general Poisson stopped sum distributions.

This revised method of deciding criticality eliminates the problem of reactions that have an infinitesimally small probability of driving their reactant species pop-



**FIG. 2:** An example critical surface for a Skellam distribution with criticality level  $\alpha = 0.001$ . The values on the  $x$ -axis represent the mean,  $\lambda_1$ , of the Poisson distribution depleting the species whereas the values on the  $y$ -axis represent the mean,  $\lambda_2$ , of the Poisson distribution regenerating the species. The surface represents the value of  $x_i$  above which species  $S_i$  is not classified as critical.

ulations negative being labeled as critical. It also ensures that reactions that have a high probability of sending reactant species negative are always labeled as critical. This allows us to approximate the number of firings of more reaction channels using Poisson random variables and fewer using the adapted SSA technique.

An algorithm for the implementation of the confidence-based methods is outlined as follows.

1. Initialize the time  $t = t_0$  and the species numbers  $\mathbf{X}(t_0) = \mathbf{x}_0$ .
2. Evaluate the propensity functions,  $a_j(\mathbf{x})$ , and their sum,  $a_0(\mathbf{x}) = \sum_{j=1}^M a_j(\mathbf{x})$ , and identify which reactions are currently critical using the method described in this section (Section III).
3. With a pre-specified value of  $\varepsilon$ , compute a candidate leap time,  $\tau'$ , using the method of Cao et al.<sup>6</sup> as described in Section II C.  $\tau'$  is the largest permissible time-step for non-critical reactions.
4. If the value of  $\tau'$  chosen is less than some small multiple (say 2) of  $1/a_0$  then reject it and implement a number (say 100) of successive steps of the SSA before returning to step (2). If  $\tau$  is larger than our chosen small multiple of  $1/a_0$  then accept it and proceed to step (5).

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5. Compute the sum  $a_0^c(\mathbf{x})$  of the critical propensity functions. Generate a second candidate leap time  $\tau''$ , in a method akin to the SSA, as a sample of an exponential random variable with mean  $1/a_0^c(\mathbf{x})$ .  $\tau''$  is a tentative estimate of the time to the next critical reaction.
6. Take  $\tau = \min\{\tau', \tau''\}$ . For all non critical reactions,  $R_j$ , generate  $k_j$  as a sample of the Poisson random variable with mean  $a_j(\mathbf{x})\tau$ .
  - (a) If  $\tau' < \tau''$ , set  $k_j = 0$  for all critical reactions (i.e. no critical reactions fire).
  - (b) If  $\tau'' < \tau'$ , use *rand*, a uniform random number between 0 and 1, to generate a reaction index,  $j_c$ , with probability  $a_{j_c}(\mathbf{x})/a_0^c(\mathbf{x})$ , in proportion to its propensity function. i.e. find  $j_c$  such that

$$\sum_{j'=1}^{j_c} a_{j'}(\mathbf{x}) < a_0^c(\mathbf{x})\text{rand} < \sum_{j'=1}^{j_c+1} a_{j'}(\mathbf{x}). \quad (14)$$

Set  $k_{j_c} = 1$ , and for all other critical reactions set  $k_j = 0$ .

7. If there is a negative component in  $\mathbf{x} + \sum_{j=1}^M k_j \boldsymbol{\nu}_j$ , reduce  $\tau'$  by half and return to step (4). Otherwise update  $\mathbf{x} = \mathbf{x} + \sum_{j=1}^M k_j \boldsymbol{\nu}_j$  and  $t = t + \tau$ .
8. If  $t < t_{final}$ , the desired stopping time, then go to step (2). Otherwise stop.

## IV. NUMERICAL EXAMPLES

In order to test the our revised  $\tau$ -leaping method we have applied it to four different systems of reactions. The first is a set of 100 isomerization reactions, the second a similar set of 100 dimerization reactions. The third is the standard LacZ/LacY system<sup>19</sup> using the model developed by Kierzek<sup>7,17,18</sup> as employed by Tian and Burrage<sup>22</sup> and Cao et al.<sup>5,6</sup> to test the accuracy and efficiency of their  $\tau$ -leaping algorithms. The fourth and final comparison is a system simulating cell migration in a one-dimensional domain using a position jump process (see Baker et al.<sup>3</sup>). When calculating a critical curve/surface in these numerical simulations

A confidence-based method for selecting species criticality in  $\tau$ -leaping

we consider the distribution of the change in species number due solely to reactions that deplete the species number:

$$\sum_{\nu_{ij} < 0, j \in J_{ncr}} \nu_{ij} \mathcal{P}_j(a_j(\mathbf{x})\tau). \quad (15)$$

In the comparisons that follow we will denote this the “Confidence-Based (CB)-depletion” method, indicating that the distribution we consider for the change in species is purely from reactions which deplete the species number. This method will use a criticality curve similar to that shown in Fig. 1. We recognize that this does not take into account the possible re-population of the species by reactions for which  $\nu_{ij} > 0$  and as such, in this method, we will be being overly cautious in our classification of critical reactions. For comparison, we also consider the distribution of the change in species number due to those reactions that deplete and those that regenerate the species number:

$$\sum_{j \in J_{ncr}} \nu_{ij} \mathcal{P}_j(a_j(\mathbf{x})\tau). \quad (16)$$

We denote this the “Confidence-Based (CB)-regeneration” method. This method will employ a criticality curve similar to that shown in Fig. 2. In general the “regeneration” method will be more efficient than the “depletion” method since by considering possible regeneration of species numbers during reactions we will obtain a tighter bound on the necessary level of criticality for each species and will classify fewer reactions, unnecessarily, as critical. However, the depletion method may be simpler to implement since the cumulative distribution function (CDF) of the Poisson distribution has a closed form and the CDF of the Skellam distribution does not. This makes calculating the criticality curve for the depletion method, using the CDF of the Poisson distribution simpler than for the regeneration method, where the probability density function of the Skellam distribution must be summed for each value of the parameter to calculate the desired curve.

In the following simulations we compare the times of the direct method implementation of the SSA, the CGP with an extensive range of values of the critical-

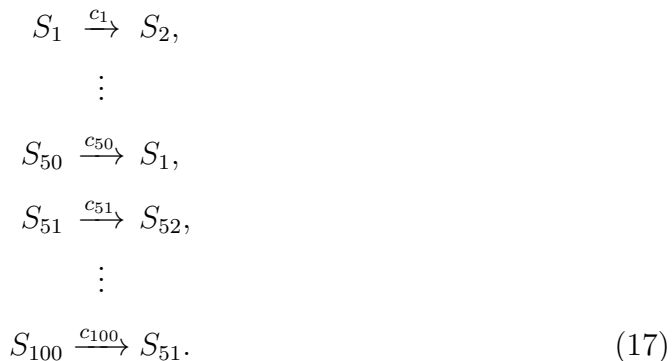


A confidence-based method for selecting species criticality in  $\tau$ -leaping

ity parameter,  $n_c = 0 \dots 20$  (approximately the range of values suggested by Cao et al.<sup>5</sup>), and the CB methods with confidence level,  $\alpha = 1 \times 10^{-7}$ . The accuracy of the CB methods is found to be comparable to that of the CGP method in all simulations (figures not shown). All simulations detailed in this section were written in C++ performed on a “no name” brand machine with 4 AMD (Advanced Micro Devices) Phenom(tm) II 945 processors (3GHz clock speed, 2MB L2 cache, 6MB L3 cache), 64-bit kernel running Ubuntu Linux 10.04 LTS.

### A. Isomerization loops

In this somewhat contrived set of reactions there are 100 reactant species and 100 reactions. These reactions form two isomerization loops. In both loops every species decays to the next until the last species decays back to the first:



All the isomerization reactions occur with the same rate constant  $c_i = 0.1$  for  $i = 1 \dots 100$ . Initially each species in the first isomerization loop has 10 molecules and each species in the second loop has 1000 (i.e.  $S_i(0) = 10$  for  $i = 1 \dots 50$  and  $S_i(0) = 1000$  for  $i = 51 \dots 100$ ). We simulate over the time interval  $t \in [0, 10]$  and repeat the simulations 1000 times.

The CB methods are the fastest in this situation with the “regeneration” method being slightly faster than the “depletion” method, as expected. There are sufficiently many of each species to make  $\tau$ -leaping more effective than the SSA, but there are a number of species which are below the criticality threshold,  $n_c = 11$ , of the CGP  $\tau$ -leaping method. The CB methods determine that these reaction channels are not,

## A confidence-based method for selecting species criticality in $\tau$ -leaping

	CPU time (s)	Steps	Critical reactions
SSA	72.93	50507096	N/A
CGP ( $n_c = 11$ )	18.93	264192	8232365
CB-depletion	2.77	31080	66544
CB-regeneration	2.74	29461	45493

**TABLE I:** A comparison, for model (17), of the total CPU time, number of steps taken and number of reactions deemed to be critical over a common time interval ( $t \in [0, 10]$ ) from a common initial condition ( $S_i(0) = 10$  for  $i = 1 \dots 50$  and  $S_i(0) = 10$  for  $i = 51 \dots 100$ ) for 1000 repeats using the SSA and three  $\tau$ -leaping methods. None of the  $\tau$ -leaping methods required the rejection of any time-steps due to negative species numbers. We choose the criticality parameter  $n_c = 11$  as the median value of the range 2 to 20 suggested by Cao et al.<sup>5</sup>.

in fact, critical as they have a minuscule probability of sending their contingent species negative. We can alter the initial conditions to show that the CB methods perform consistently well in comparison to the SSA and the CGP  $\tau$ -leaping method.

For example, if we set the initial number of each species to be 10 (i.e.  $S_i(0) = 10$  for  $i = 1 \dots 100$ ) then we see that the SSA out-performs all three  $\tau$ -leaping algorithms (see table II). It out-performs the CGP  $\tau$ -leaping method by more than an order of magnitude, but only marginally out-performs the CB methods.

	CPU time (s)	Steps	Critical reactions
SSA	1.40	1001664	N/A
CGP ( $n_c = 11$ )	37.75	529277	33053214
CB-depletion	2.65	34017	127148
CB-regeneration	2.41	31666	83179

**TABLE II:** A comparison, for model (17), of the total CPU time, number of steps taken and number of reactions deemed to be critical over a common time interval ( $t \in [0, 10]$ ) from a common initial condition ( $S_i(0) = 10$  for  $i = 1 \dots 100$ ) for 1000 repeats using the SSA and three  $\tau$ -leaping methods. The SSA only marginally out-performs the CB methods, but both the CB method and the SSA drastically out-perform the CGP method.

If we set the initial number of each species to be 1000 (i.e.  $S_i(0) = 1000$  for  $i = 1 \dots 100$ ) we see that the CB methods are nearly two orders of magnitude faster than the SSA and of comparable (or slightly increased) efficiency with the CGP method (see table III). For this reaction system the CB methods demonstrate more versatility than the traditional one-size-fits-all approach of the CGP algorithm.

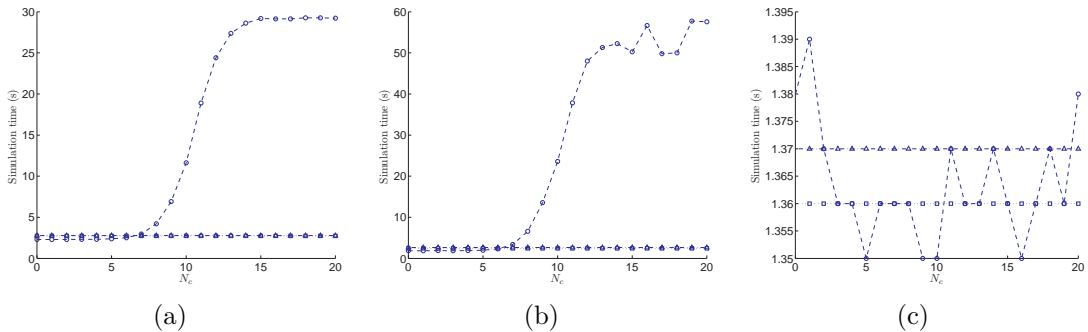
Figure 3 demonstrates that the CB methods perform consistently well in com-

## A confidence-based method for selecting species criticality in $\tau$ -leaping

	CPU time (s)	Steps	Critical reactions
SSA	127.32	100004782	N/A
CGP ( $n_c = 11$ )	1.38	3830	0
CB-depletion	1.37	3818	0
CB-regeneration	1.36	3789	0

**TABLE III:** A comparison, for model (17), of the total CPU time, number of steps taken and number of reactions deemed to be critical over a common time interval ( $t \in [0, 10]$ ) from a common initial condition ( $S_i(0) = 1000$  for  $i = 1 \dots 100$ ) for 1000 repeats using the SSA and three  $\tau$ -leaping methods.

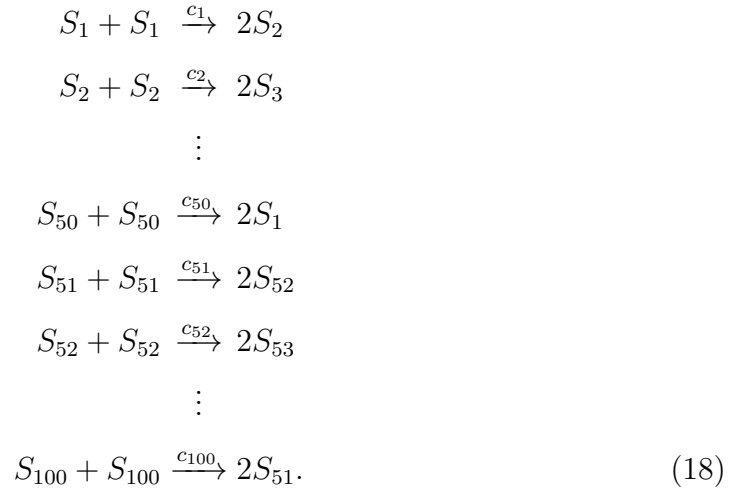
parison to the CGP technique over a range of values of the criticality parameter,  $n_c$ . At worst the speeds of the two algorithms are comparable and at best the CB algorithms are considerably faster than the CGP algorithm. These plots demonstrate that the CB methods are a robust choice in the face of differing initial conditions and crucially their performance is independent of any tuning parameters.



**FIG. 3:** A comparison of simulation times for 1000 repeats of each of the three  $\tau$ -leaping methods for each of the three initial conditions described in tables I, II and III: (a)  $S_i(0) = 10$  for  $i = 1 \dots 50$  and  $S_i(0) = 1000$  for  $i = 51 \dots 100$ , (b)  $S_i(0) = 10$  for  $i = 1 \dots 100$ , (c)  $S_i(0) = 1000$  for  $i = 1 \dots 100$ , over the range of values of the parameter  $n_c = 0 \dots 20$ . Circles joined by a dashed line correspond to the CGP method, triangles joined by a dot-dash line to the CB-depletion method and squares joined by a dotted line to the CB-regeneration method. In (a) and (b), for lower values of  $n_c$ , the simulation times of all three algorithms are comparable, however, for larger values of  $n_c$  the CB methods are significantly faster. In (c) all three methods are approximately comparable independent of the value of  $n_c$ .

## B. Dimerization loops

In order to show that the CB methods can be applied straight-forwardly to systems of non-linear reactions we have altered the above reaction system, to be dimerizations (instead of isomerizations) where two molecules of each reactant species are required for each reaction. These reactions form two dimerization loops. In each loop one molecule of a species combines with another of the same species and decays to two molecules of the next species until molecules of the last species decay back to the first:



All the dimerization reactions occur with the same rate constant  $c_i = 0.1$  for  $i = 1 \dots 100$ . Initially each species in the first dimerization loop has 10 molecules and each species in the second loop has 1000 molecules (i.e.  $S_i(0) = 10$  for  $i = 1 \dots 50$  and  $S_i(0) = 1000$  for  $i = 51 \dots 100$ ). We use this set of reactions to test the speed and reliability of the algorithms. We simulate over the time interval  $[0, 10]$  and repeat the simulations 1000 times.

Clearly the CB methods are faster than the CGP in the situation described in Table IV for similar reasons to those given for the isomerization loop system. Altering the initial conditions we will see that the CB methods perform consistently well in comparison to the SSA and the CGP  $\tau$ -leaping method. If we set the initial number of each species to be large for both dimerization loops; 1000, for example (i.e.  $S_i(0) = 1000$  for  $i = 1 \dots 100$ ) then we see that all three  $\tau$ -leaping methods

## A confidence-based method for selecting species criticality in $\tau$ -leaping

	CPU time (s)	Steps	Critical reactions
SSA	39706	3463378894	N/A
CGP ( $n_c = 11$ )	398	2468173	123345100
New	320	972062	13492169
New	313	898838	7982245

**TABLE IV:** A comparison, for model (18), of the total CPU time, number of steps taken and number of reactions deemed to be critical over a common time interval ( $t \in [0, 10]$ ) from a common initial condition ( $S_i(0) = 10$  for  $i = 1 \dots 50$  and  $S_i(0) = 1000$  for  $i = 51 \dots 100$ ) for 1000 repeats using the SSA and three  $\tau$ -leaping methods. None of the  $\tau$ -leaping methods required the rejection of any time-steps due to negative species numbers.

are well over an order of magnitude faster than the SSA. Both CB methods remain marginally more efficient than the CGP method (see table V).

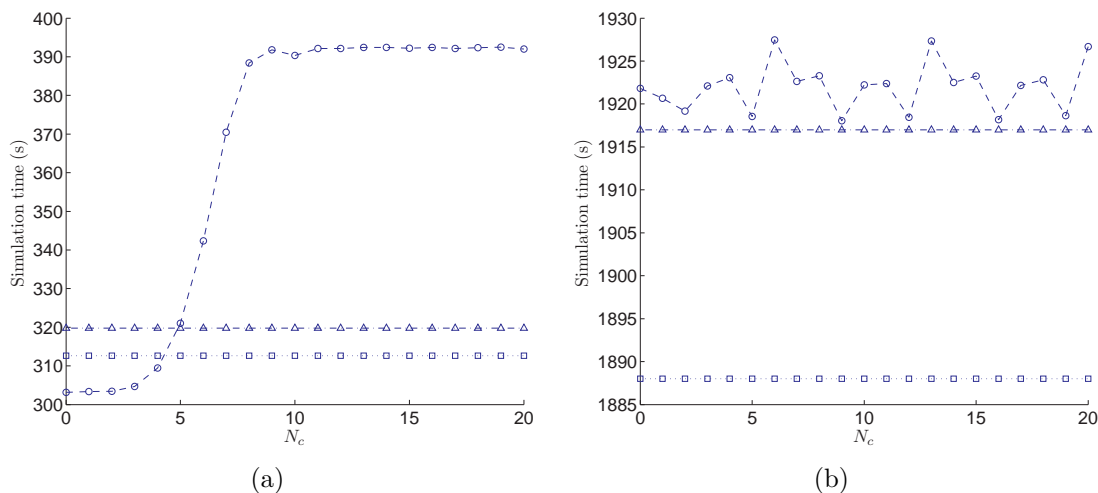
	CPU time (s)	Steps	Critical reactions
SSA	70402	2516518253	N/A
CGP ( $n_c = 11$ )	1923	19979926	0
CB-depletion	1917	19980419	0
CB-regeneration	1888	19979825	0

**TABLE V:** A comparison, for model (18), of the total CPU time, number of steps taken and number of reactions deemed to be critical over a common time interval ( $t \in [0, 10]$ ) from a common initial condition ( $S_i(0) = 1000$  for  $i = 1 \dots 100$ ) for 1000 repeats using the SSA and three  $\tau$ -leaping methods.

### C. LacY and LacZ expression model

The genetic regulation of the lac operon was one of the earliest complex genetic regulatory mechanisms to be described in detail. The lac operon consists of a promoter, a terminator, regulator, operator and three structural genes. The two most important of these structural genes are LacY and LacZ, necessary for lactose catabolism<sup>19</sup>. The other constituents of the lac operon control the expression of LacY and LacZ via a series of interactions with transcription regulators in the cytosol. The number of transcription regulators in the system may be as low as ten and these transcription regulators bind to a single ‘molecule’ of the DNA regulatory region<sup>19</sup>. Clearly stochastic fluctuations of molecule numbers and time intervals will

## A confidence-based method for selecting species criticality in $\tau$ -leaping



**FIG. 4:** A comparison of simulation times for 1000 repeats of for each of the three  $\tau$ -leaping methods for each of the initial conditions described in tables IV and V: (a)  $S_i(0) = 10$  for  $i = 1 \dots 50$  and  $S_i(0) = 1000$  for  $i = 51 \dots 100$  and (b)  $S_i(0) = 1000$  for  $i = 1 \dots 100$ , over a range of values of the parameter  $n_c = 0 \dots 20$ . Legend is as described in the caption of Fig. 3. In (a) we see that for lower values of  $n_c$  the CGP method does slightly better than the CB methods, however, for larger values of  $n_c$  the CB methods are significantly faster. In (b) the CB methods are marginally faster than the CGP method independent of the value of  $n_c$ .

be important in such a system and the near-zero copy numbers of some species make this system a good test of  $\tau$ -leaping methods aiming to avoid negative populations. The LacZ/LacY model as developed by Kierzek<sup>18</sup>, consists of 18 reactant species, one product (a result of the catabolization of lactose which does not take part, as a reactant, in any of the system’s reactions) and 22 reaction channels. A list of reaction channels and rates of the chemical kinetics can be found in Tian and Burrage<sup>22</sup>.

Running the SSA for this reaction set from  $t = 0$  to  $t = 2000$  (the time interval used for algorithm comparisons in Tian and Burrage<sup>22</sup>) takes over 6 minutes on our computer. Since running large numbers of repeats will require a large amount of computer time we instead run the SSA from  $t = 0$  to  $t = 1000$  to find an ‘initialization state’ for the system and run 1000 repeats of each simulation algorithm from  $t = 1000$  to  $t = 1001$ , as in Cao et al.<sup>6</sup>. The numbers of molecules of each species in the initialization state are given in table VI.

The results in table VII demonstrate that the CGP method is the quickest, closely

## A confidence-based method for selecting species criticality in $\tau$ -leaping

Species	$S_1$	$S_2$	$S_3$	$S_4$	$S_5$	$S_6$	$S_7$	$S_8$	$S_9$	$S_{10}$
Number	0	28	0	1	0	22	0	1	0	392
Species	$S_{11}$	$S_{12}$	$S_{13}$	$S_{14}$	$S_{15}$	$S_{16}$	$S_{17}$	$S_{18}$	$S_{19}$	
Number	59	57	1661	662	17760	15832	6814877	155	78727744	

**TABLE VI:** Initial numbers of molecules of each of the 19 species in the LacZ/LacY model taken from one run of the SSA from  $t = 0$  to  $t = 1000$ .

followed by the CB-depletion and CB-regeneration  $\tau$ -leaping algorithms. Both the  $\tau$ -leaping methods are an order of magnitude faster than the SSA. Very few of the species have the sorts of numbers of molecules for the CB methods of criticality-selection to make a considerable difference over the CGP method (see table VI). Some are too large, meaning that both CGP and CB methods will classify the dependent reactions as non-critical, and some are too small, meaning that both methods are likely to classify the dependent reactions as critical. The CB methods turn out to be slightly slower since they do not gain any advantage from differential classifications of criticality (see Critical reactions column of table VII). However, all three  $\tau$ -leaping methods are still considerably faster than the SSA over the chosen time-period (see table VII).

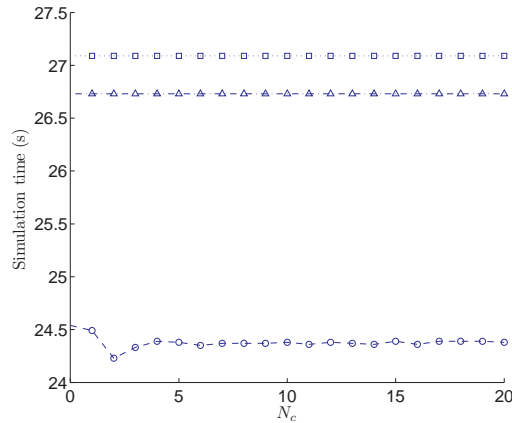
	CPU time (s)	Steps	Critical reactions
SSA	254.32	448740253	N/A
CGP ( $n_c = 11$ )	24.56	3904290	13662309
CB-depletion	26.73	3902985	13588212
CB-regeneration	27.09	3905514	13608898

**TABLE VII:** A comparison, for the LacZ/LacY model (17) of Kierzek<sup>17</sup>, of the total CPU time, number of steps taken and number of reactions deemed to be critical over a common time interval ( $t \in [1000, 1001]$ ) from a common initial condition (see table VI) for 1000 repeats using the SSA and three  $\tau$ -leaping methods.

### D. A further example from biology

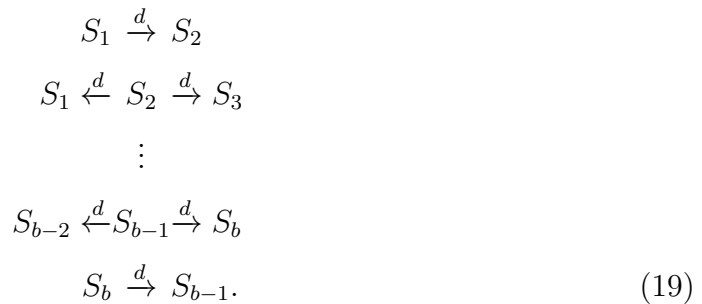
The final system we consider is a one-dimensional position-jump model of cell migration<sup>3,21</sup>. The premise of the simulation is the time evolution of discrete cell density given an initial profile. The stochastic motion of individual cells is modeled

## A confidence-based method for selecting species criticality in $\tau$ -leaping



**FIG. 5:** A comparison of simulation times for 1000 repeats of each of the three  $\tau$ -leaping methods for the LacZ/LacY model over a range of values of the parameter  $n_c = 0 \dots 20$ . For all values of  $n_c$  the CGP method is marginally quicker than either of the CB methods.

across a domain with zero-flux boundary conditions. We divide the unit domain  $[0, 1]$  into  $b = 50$  intervals of equal length and implement migration by allowing cells to move left and right from their current interval with constant transition rate,  $d = 1$ . We assume there is no cell death or division on the time-scale of interest so that, in combination with the zero-flux boundary conditions, the total cell numbers remain constant. Essentially, this example reduces to a system of  $b = 50$  species reacting through  $2 \times b - 2 = 98$  reaction channels (cells moving left and right from each interval except for at the end intervals where cells are only allowed to move in one direction to implement zero flux boundary conditions). The number of cells in each interval corresponds to the number of molecules of each species. As such all reactions are isomerizations and propensity functions depend only on the transition rate,  $d$ , and the number of cells in the corresponding interval. We can write the reaction system as follows:





## A confidence-based method for selecting species criticality in $\tau$ -leaping

We consider a variety of conditions to determine how the algorithms perform against each other. In the first example we place 5000 cells in the first interval of the domain (i.e.  $S_1(0) = 5000$  and  $S_i(0) = 0$  for  $i = 2 \dots, 50$ ). The system is run over the time interval  $[0, 2000]$  and results are given in Table VIII.

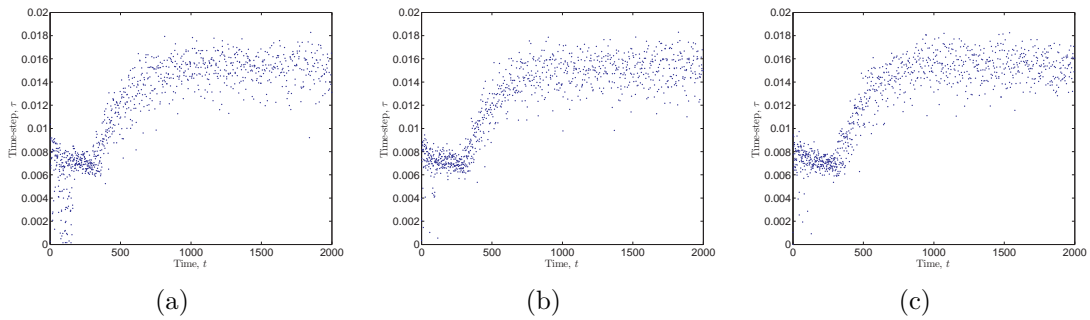
	CPU time (s)	Steps	Critical reactions
SSA	34834	$2.72 \times 10^9$	N/A
CGP ( $n_c = 11$ )	7542	$1.71 \times 10^8$	$5.20 \times 10^8$
CB-depletion	7310	$1.66 \times 10^8$	$6.86 \times 10^8$
CB-regeneration	7160	$1.65 \times 10^8$	$3.31 \times 10^8$

**TABLE VIII:** A comparison, for model (19), of the total CPU time, number of steps taken and number of reactions deemed to be critical over a common time interval ( $t \in [0, 2000]$ ) from a common initial condition ( $S_1(0) = 5000$  and  $S_i(0) = 0$  for  $i = 2 \dots 50$ ) for 1000 repeats using the SSA and three  $\tau$ -leaping methods.

Table VIII demonstrates the improved efficiency of the CB methods in comparison to the CGP method. The simulation time is reduced by approximately 3-5%. This is evidenced by the smaller number of steps taken by the CB methods. Although it appears that the CGP has fewer critical reactions, this is an artifact of our recording procedure: critical reactions are not recorded during the time the  $\tau$ -leaping simulations spend implementing the SSA (when the proposed time-step,  $\tau'$ , given by non-critical reactions is smaller than twice the average time-step of the SSA,  $2/a_0$ , (see Step 4 of the algorithm given in Section III)). The CGP algorithm spends far more time implementing the SSA, as evidenced by the increased simulation time and number of steps in comparison to the CB methods. Similar reasoning applies to the results in Table 7.

Figure 6 displays the size of the time-step,  $\tau$ , against the time it was chosen. Early in the simulations there is usually at least one species with low molecular numbers (i.e. an interval with a small number of cells) and the CGP method marks a large proportion of reactions dependent on low copy-number species as being critical, despite their minuscule probability of driving the species number negative. This results in a choice of small  $\tau$  (see Fig. 6 (a)). However, the CB methods are freer to classify reactions dependent on low copy number species as non-critical. Far fewer small values of  $\tau$  are selected in the initial stages of the simulations using the CB

## A confidence-based method for selecting species criticality in $\tau$ -leaping



**FIG. 6:** For a simulation of the one-dimensional cell migration reactions of model (19) the values of the chosen time-step,  $\tau$ , vs the time it was chosen, for (a) the CGP  $\tau$ -selection procedure, (b) the CB-depletion procedure and (c) the CB-regeneration procedure.  $\tau$  values were taken every 1000<sup>th</sup> leap (up to a maximum of 1000 samples). Other conditions are as given in table VIII.

methods (see Fig. 6 (b) and 6(c)) allowing the simulations to run to completion in a shorter time (see Table VIII).

The difference between the criticality classification methods is even more stark when we simulate the same reaction model with slightly altered conditions. Consider doubling the spatial resolution of the interval (by doubling the number of intervals and halving the interval width) i.e.  $b = 100$ . Consequently, in order to maintain the same steady state cell numbers in each interval, we also double the initial number of cells i.e.  $S_1(0) = 10000$  and  $S_i(0) = 0$  for  $i = 2 \dots 50$ . We now have a reaction system of 100 chemical species reacting through 198 reaction channels. Table IX highlights the improved efficiency of the CB methods in comparison to the CGP method whilst at the same time it maintains its advantage over the SSA. This further demonstrates the robustness of the CB methods as a parameter-independent choice for stochastic acceleration.

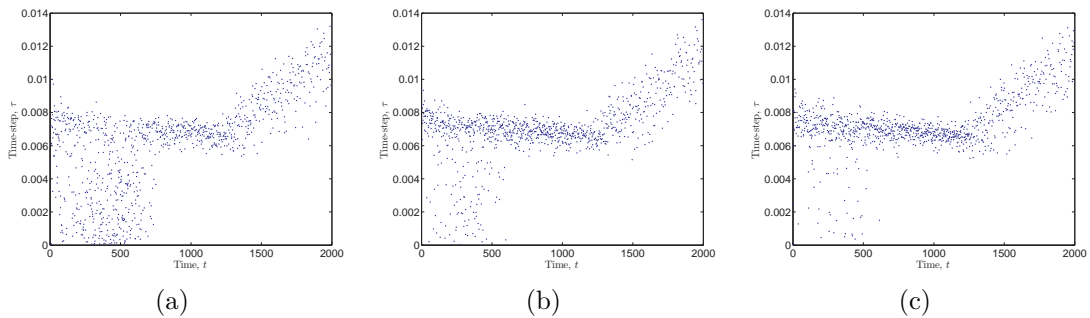
Figure 7 shows the analogous comparison of time-step,  $\tau$ , to Fig. 6 for the revised conditions described above. The CGP method is overly-restrictive in its choice of time-step for an even larger proportion of the simulation than in Fig. 6. This trend continues as we increase the spatial resolution of the system until the CGP method is overly restrictive in time-step for the duration of the simulation, increasing the discrepancy in times between the CGP and CB  $\tau$ -leaping methods.

As with the other model systems, in Fig. 8, we provide a comparison of the three

## A confidence-based method for selecting species criticality in $\tau$ -leaping

	CPU time (s)	Steps	Critical reactions
SSA	13538	$4.00^9$	N/A
CGP ( $n_c = 11$ )	4497	$3.27 \times 10^7$	$5.53 \times 10^8$
CB-depletion	3851	$2.78 \times 10^7$	$5.96 \times 10^8$
CB-regeneration	3762	$2.71 \times 10^7$	$2.79 \times 10^8$

**TABLE IX:** A comparison, for model (19) (now with  $b = 100$  intervals), of the total CPU time, number of steps taken and number of reactions deemed to be critical over a common time interval ( $t \in [0, 2000]$ ) from a common initial condition ( $S_1(0) = 10000$  and  $S_i(0) = 0$  for  $i = 2 \dots 50$ ) for 100 repeats using the SSA and three  $\tau$ -leaping methods.



**FIG. 7:** For a simulation of the one-dimensional cell migration reactions of model (19) the values of the chosen time-step  $\tau$  vs the time it was chosen, for (a) the CGP  $\tau$ -selection procedure, (b) the CB-depletion procedure and (c) the CB-regeneration procedure.  $\tau$  values were taken every  $1000^{\text{th}}$  leap (up to a maximum of 1000 samples). Other conditions are as in Table IX

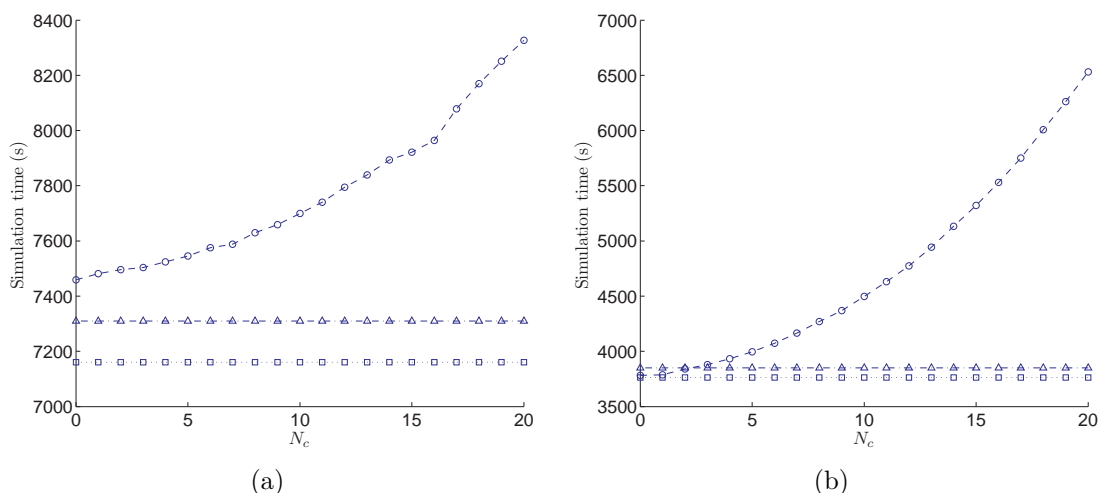
$\tau$ -leaping algorithms for varying values of the criticality parameter,  $n_c$ . The CB methods are shown to be either comparable or superior to the CGP method as  $n_c$  varies.

As a final demonstration of the efficiency of the CB method, Fig. 9 shows the average time taken per simulation for varying numbers of cells initially positioned in the first interval of 50. The CB-depletion method is quicker in all simulations and in some cases substantially so.

## V. DISCUSSION

The CGP method for determining criticality takes a one-size-fits-all approach by allocating a critical value  $n_c$ , for  $L_j$  values below which reaction channel  $j$  is classified as critical. As demonstrated in Section III, by considering a simple degradation

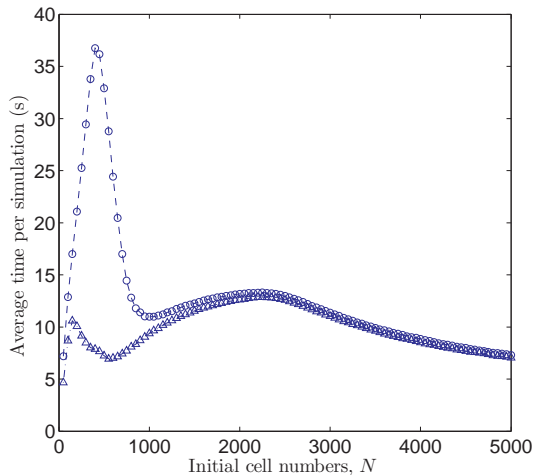
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**FIG. 8:** A comparison of simulation times for each of the three  $\tau$ -leaping methods for both of the initial conditions described above: (a)  $b = 50$ ,  $S_1(0) = 5000$  and (b)  $b = 100$ ,  $S_1(0) = 10000$  over a range of values of the parameter  $n_c = 0 \dots 20$ . Legend is as described in the caption of Fig. 3. In (a) the CB methods are significantly faster than the CGP method. Times given are for 1000 repeats of the simulation. The higher the value of  $n_c$  the more efficient the CB methods become in comparison to the CGP method. In (b) we see that for very low values of  $n_c$  the CGP and CB methods are of comparable speed, however, for larger values of  $n_c$  the CB methods are significantly faster. Times given are for 100 repeats of the simulation.

reaction, the speed and accuracy of the CGP method is dramatically dependent on the value of this parameter. If chosen too high it can be overly restrictive. If chosen too low there is a danger of species numbers becoming negative. We have presented a more versatile method of classifying criticality of reaction channels. We consider the *species* numbers and calculate how likely it is that a species will be driven negative given the reactions that deplete and replenish its numbers. We can then classify an individual species as critical and consequently all reactions dependent on that species are also classified as critical. Our confidence-based approach allows us to be more discriminatory about which species, and hence reactions, are considered critical. Only those species having a pre-specified probability of becoming negative are classified as critical. This flexible approach leads to the classification of fewer reactions as critical, enabling the simulation to select more and larger time-steps from the non-critical regime. This method does not face the problem of having to tune the value of  $n_c$  for the relevant simulation so we need not worry that we will send the population of a reaction species negative through incaution. This makes

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**FIG. 9:** Average CPU time taken (in seconds) given different numbers of cells initially positioned in the first interval on a domain partitioned into  $b = 50$  intervals. The initial cell numbers range from  $N = 50$  to  $N = 5000$  in increments of 50. All times are averaged over 10 repeats. Circles with a dashed line represent the CGP method ( $n_c = 11$ ) whilst triangles with a dot-dashed line the CB-depletion method. The CB-regeneration method is of comparable speed to the CB-depletion method and for clarity is not shown.

our method a consistent choice, robust to a wide variety of initial conditions.

Test simulations carried out on four model reaction systems have indicated that the CB  $\tau$ -leaping procedures can be orders of magnitude faster than the CGP method in some situations. It appears that in all situations the CB methods will be at least of comparable speed to the CGP method with comparable accuracy. It is important to emphasize that the CB methods achieve this optimal or near-optimal performance without the necessity for the tuning parameter,  $n_c$ . This will obviate the need for running expensive test simulations to optimize the value of  $n_c$ .

We have found the accuracy of the CB methods to be comparable to that of the CGP methods in all of the simulations we have considered. An interesting further investigation of the accuracy of both  $\tau$ -leaping strategies may be to consider a non-homogeneous variation on the cell migration algorithm presented in Section IV D: The Fisher, Kolmogorov, Petrovski, Piskunov wave front, for example, has a speed which is extremely sensitive to small perturbations. Incorrect simulation of species numbers should have macroscopic consequences on the wave speed<sup>4,14</sup>.

Finally we must acknowledge that one possible cause of erroneous classification

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of criticality which may occur in the CB methods (and hence a possible reduction in speed of the algorithms) is due to the fact that we are forced to use the time-step,  $\tau$ , from the previous step of the algorithm in order to approximate the distribution in the change of species number for the current step. We justified this approximation, by appealing to the leap-condition: that propensity functions, and hence the proposed time-step  $\tau'$ , will not change significantly between reactions. However, there is likely to be some degree of change which will lead to erroneous classification. One possible way to circumvent this problem would be to iteratively choose  $\tau$  and species criticality in a manner similar to that implemented by Harris and Clancy<sup>15</sup> when classifying reactions in their “partitioned leaping” approach: Start with the value of  $\tau$  from the previous time-step and classify reactions as critical or otherwise based on this  $\tau$ . Then update  $\tau$  according to the criticality status of the reaction channels. Return and reclassify the reactions using this updated value of  $\tau$ . Repeat this process until reaction classifications cease to change. Whether this iterative method of  $\tau$ -selection would converge quickly and whether the advantaged gained from the precise classification of reactions would outweigh the cost of the iterative procedure remain unexplored areas for further investigation.

We suggest that our confidence-based method of species and hence reaction criticality classification is sufficient to increase the speed of many systems of reactions and will at the very least be a robust choice of algorithm in the face of widely varying species populations. The confidence-based method of choosing criticality will perform particularly well when there are some species with large numbers of molecules and some with smaller (formerly CGP sub-critical (i.e.  $S_i < n_c$ )) numbers. This will confer the benefits of  $\tau$ -leaping whilst avoiding the handicap of classifying too many reaction channels as critical and decelerating the algorithm.

## VI. APPENDICES

### A. Proof of Property 2

The probability that the difference of the two random variables  $\mathcal{P}_1 - \mathcal{P}_2$  (which we will now denote by  $\mathcal{SK}$  in this derivation) takes the value  $k$  is the sum from

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$j = 0 \dots \infty$  of the probability that the first random variable,  $\mathcal{P}_1$ , takes the value  $k + j$  multiplied by the probability that the second random variable,  $\mathcal{P}_2$ , takes the value  $j$ . Using the definition of the probability density function of the Poisson random variable we can rewrite the above more mathematically as:

$$\Pr(\mathcal{SK} = k) = \sum_{j=0}^{\infty} \frac{e^{-\lambda_1} \lambda_1^{(k+j)}}{(k+j)!} \times \frac{e^{-\lambda_2} \lambda_2^j}{j!}. \quad (20)$$

This can be simplified in a few lines to

$$\begin{aligned} \Pr(\mathcal{SK} = k) &= e^{-[\lambda_1 + \lambda_2]} \left( \frac{\lambda_1}{\lambda_2} \right)^{k/2} \sum_{j=0}^{\infty} \frac{(\lambda_1 \lambda_2)^{(k/2+j)}}{(k+j)! j!}, \\ &= e^{-[\lambda_1 + \lambda_2]} \left( \frac{\lambda_1}{\lambda_2} \right)^{k/2} I_k(2\sqrt{\lambda_1 \lambda_2}), \end{aligned} \quad (21)$$

where  $I_k(z)$  is the modified Bessel function of the first kind.

## B. Proof of Property 3

We prove Property 3 using PGFs. The PGF of the sum of a Poisson  $m$ -let and a Poisson  $n$ -let is given by

$$\begin{aligned} G(z) &= E(z^{\mathcal{P}^m + \mathcal{P}^n}) \\ &= G_{\mathcal{Q}_1}(z^m) G_{\mathcal{Q}_2}(z^n) \\ &= e^{\lambda_1(z^m - 1)} \times e^{\lambda_2(z^n - 1)}, \\ &= \exp\{\lambda_1 z^m + \lambda_2 z^n - (\lambda_1 + \lambda_2)\}, \end{aligned} \quad (22)$$

where  $\mathcal{Q}_1$  and  $\mathcal{Q}_2$  are Poisson distributions with means  $\lambda_1$  and  $\lambda_2$ . The first equality makes use of the assumption that  $\mathcal{P}^m$  and  $\mathcal{P}^n$  are independent. The last line of equation (22) is the PGF of a Poisson stopped sum distribution.

## ACKNOWLEDGMENTS

CAY would like to thank EPSRC and BBSRC for funding via the Systems Biology Doctoral Training Centre, University of Oxford.

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