

Breakdown of the reaction-diffusion master equation with nonelementary rates

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(Received 21 December 2015; published 19 May 2016)

The chemical master equation (CME) is the exact mathematical formulation of chemical reactions occurring in a dilute and well-mixed volume. The reaction-diffusion master equation (RDME) is a stochastic description of reaction-diffusion processes on a spatial lattice, assuming well mixing only on the length scale of the lattice. It is clear that, for the sake of consistency, the solution of the RDME of a chemical system should converge to the solution of the CME of the same system in the limit of fast diffusion: Indeed, this has been tacitly assumed in most literature concerning the RDME. We show that, in the limit of fast diffusion, the RDME indeed converges to a master equation but not necessarily *the* CME. We introduce a class of propensity functions, such that if the RDME has propensities exclusively of this class, then the RDME converges to the CME of the same system, whereas if the RDME has propensities not in this class, then convergence is not guaranteed. These are revealed to be elementary and nonelementary propensities, respectively. We also show that independent of the type of propensity, the RDME converges to the CME in the simultaneous limit of fast diffusion and large volumes. We illustrate our results with some simple example systems and argue that the RDME cannot generally be an accurate description of systems with nonelementary rates.

DOI: [10.1103/PhysRevE.93.052135](https://doi.org/10.1103/PhysRevE.93.052135)**I. INTRODUCTION**

The chemical master equation (CME) describes the fluctuations of molecule numbers in reactive chemical systems which are dilute and well mixed. In particular, it assumes that the probability of two particles reacting with each other is independent of their relative positions in space, which is strictly true only if diffusion rates are infinitely large, i.e., well-mixed conditions. The CME has in fact been derived from a microscopic physical description under these conditions, if mass-action kinetics are assumed [1], and is also known to be correct for nonelementary reactions in quasiequilibrium conditions [2,3].

The applicability of the CME to understand intracellular processes is limited because experiments show that diffusion coefficients inside cells are typically considerably smaller than *in vitro* due to macromolecular crowding and other effects [4]. The reaction-diffusion master equation (RDME) generalizes the CME, in an approximate way to include diffusion. Space is partitioned into small volume elements (“voxels”) of equal volume, each considered to be well mixed (although globally the space is not well mixed). Chemical reactions occur in each voxel, and diffusion of chemicals occurs as a hopping of particles between neighboring voxels. The RDME is the Markovian description of this lattice-based reaction-diffusion system. Unlike the CME, the RDME currently has no rigorous microscopic physical basis but can be justified intuitively. It is known to be accurate (compared to the continuum spatial description of Brownian dynamics) for all voxel sizes for systems consisting only of monomolecular reactions and for

a particular range of voxel sizes for systems with bimolecular reactions [5–8]. A recently introduced variant, the CRDME, modifies the way the RDME treats bimolecular reactions such that it is accurate for small voxel sizes [9].

The RDME and the CME describe the same systems, but the RDME claims greater accuracy in the sense that it contains all the information of the CME while incorporating local spatial effects which are beyond its scope. Since we know the CME to be valid if diffusion rates are fast [1], a useful test of the validity of the RDME is that it should converge to the CME in the limit of infinite diffusion rates. This convergence seems intuitively likely: If diffusion rates are fast, then particles hop between voxels much more frequently than they react, and so the well-mixedness assumption of the CME should be recovered.

In this paper, we prove that the RDME converges to a master equation in the limit of fast diffusion, but remarkably, under certain conditions, this master equation is not *the* CME. The accuracy of the RDME under these conditions is therefore called into question. The paper is organized in the following way. In Sec. II we derive an expression for the master equation to which the RDME converges in the limit of fast diffusion. We subsequently define a class of reaction types (and their corresponding propensity functions) which we call *convergent propensity functions* with the following property: *If a chemical system has exclusively convergent propensity functions, then the RDME will converge to the CME of the same system in the limit of fast diffusion.* If a chemical system has any nonconvergent propensity functions, then it will almost surely not converge to the correct CME. In Sec. III we show that elementary reactions (including zero-, first-, and second-order reactions) are in the convergent class, while more complex reactions (including Michaelis-Menten and Hill-type) are of the nonconvergent class. In Sec. IV we illustrate our results by applying them to two simple systems: one convergent and one nonconvergent. We conclude with a summary and discussion in Sec. V.

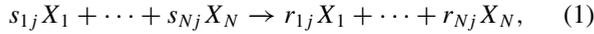
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II. PROOF

In this section we introduce the CME and the RDME and prove that the latter may or may not converge to the former in the limit of fast diffusion. We further prove that, independent of the type of propensity, the RDME still converges to the CME in the limit of fast diffusion and of large volumes, taken simultaneously.

A. The CME

Consider a well-mixed compartment of volume Ω in which there is a chemical system consisting of N chemical species, X_1, \dots, X_N involved in R possible chemical reactions where the j th reaction has the form:



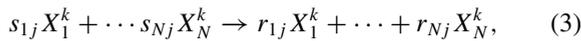
where r_{ij} and s_{ij} are the stoichiometric coefficients. The stochastic dynamics of such a system is Markovian and can be described by the CME:

$$\frac{d}{dt}P(\vec{n}, t) = \sum_{j=1}^R \left(\prod_{i=1}^N E_i^{s_{ij}-r_{ij}} - 1 \right) \hat{a}_j(\vec{n}, \Omega) P(\vec{n}, t), \quad (2)$$

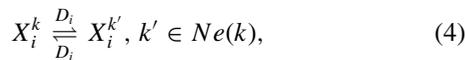
where $\vec{n} = (n_1, \dots, n_N)^T$ is the vector of molecule numbers of species X_1, \dots, X_N , respectively, $P(\vec{n}, t)$ is the probability that the system is in the state \vec{n} at time t , E_i^x is the operator which replaces n_i with $n_i + x$, and $\hat{a}_j(\vec{n}, \Omega)$ is the *propensity function* of reaction j . The propensity function is formally defined as follows: Given that the system is in state \vec{n} , then $\hat{a}_j(\vec{n}, \Omega)dt$ is the probability that a reaction of index j occurs somewhere in the volume Ω in the next infinitesimal time interval $[t, t + dt)$ [10].

B. The RDME

Consider the same chemical system as defined by (1), but now taking place in a volume of space Ω which is divided into M voxels, each of volume $\frac{\Omega}{M}$. The j th chemical reaction in voxel k will have the form:



where X_i^k refers to species X_i locally in voxel k . Note that because the stoichiometric coefficients s_{ij} and r_{ij} are voxel independent, the j th chemical reaction in a given voxel is of the same type as the j th chemical reaction in any other voxel. The diffusive interchange of chemicals between neighboring voxels is modelled by the reactions:



where D_i is the diffusion rate (the diffusion coefficient divided by the square of the lattice spacing) of species X_i (which is independent of the voxel index and hence implies the assumption that the diffusion coefficient of a given species is space independent) and $Ne(k)$ is the set of voxels neighboring k . The specific neighbors of a voxel depend on the topology of the lattice, though for the purposes of this paper it does not matter what this is, as long as every voxel is indirectly connected to every other by some path. The stochastic

dynamics of this system is described by the RDME:

$$\begin{aligned} \frac{d}{dt}P(\vec{n}^1, \dots, \vec{n}^M, t) &= \sum_{k=1}^M \sum_{j=1}^R \left(\prod_{i=1}^N E_{i,k}^{s_{ij}-r_{ij}} - 1 \right) \hat{a}_j\left(\vec{n}^k, \frac{\Omega}{M}\right) \\ &\times P(\vec{n}^1, \dots, \vec{n}^M, t) \\ &+ \sum_{k=1}^M \sum_{k' \in Ne(k)} \sum_{i=1}^N (E_{i,k}^1 E_{i,k'}^{-1} - 1) D_i n_i^k \\ &\times P(\vec{n}^1, \dots, \vec{n}^M, t), \end{aligned} \quad (5)$$

where n_i^k is the number of molecules of species X_i^k , $\vec{n}^k = (n_1^k, \dots, n_N^k)^T$, $P(\vec{n}^1, \dots, \vec{n}^M, t)$ is the probability of the system being in state $(\vec{n}^1, \dots, \vec{n}^M)$ at time t , and $E_{i,k}^x$ is the operator which replaces n_i^k with $n_i^k + x$. Note that the first two lines of Eq. (5) refer to the chemical reactions while the third and fourth lines refer to the diffusive reactions. The local propensity function is defined as follows: Given that the state of voxel k is \vec{n}^k , then $\hat{a}_j(\vec{n}^k, \frac{\Omega}{M})dt$ is the probability that one reaction of index j occurs somewhere inside this voxel in the next infinitesimal time interval $[t, t + dt)$.

C. The RDME in the limit of fast diffusion

We now investigate what happens to the RDME in the limit where $D_i \rightarrow \infty$ for all $i = 1, \dots, N$. Suppose that the system is in state $(\vec{n}^1, \dots, \vec{n}^M)$ at time t , and define $n_i = n_i^1 + \dots + n_i^M$ as the global molecule number of the species X_i . Each time a chemical reaction occurs somewhere in space, the local molecule number of one or more species changes, leading to a corresponding change in the global number of molecules of the concerned species. Before the next chemical reaction occurs, diffusive reactions will happen a very large number of times such that the system will approach the steady state of the purely diffusive system (4). Specifically, suppose that a chemical reaction just occurred somewhere in space and that the global state vector is (n_1, n_2, \dots, n_N) . Then it follows that, due to the effect of infinitely fast diffusion, the probability of having n_i^k molecules of species X_i in voxel k , conditional on the fact that there are n_i molecules of the same species in all of space, is given by the binomial distribution:

$$\begin{aligned} P(n_i^k | n_i) &= \frac{n_i!}{n_i^k!(n_i - n_i^k)!} \left(\frac{1}{M}\right)^{n_i^k} \left(1 - \frac{1}{M}\right)^{n_i - n_i^k}, \\ &i = 1, \dots, N. \end{aligned} \quad (6)$$

It also follows that the distribution of molecule numbers of all chemical species in voxel k , conditional on the global state vector, is given by:

$$P(\vec{n}^k | \vec{n}) = \prod_{i=1}^N P(n_i^k | n_i). \quad (7)$$

Note that this distribution does take into account any implicit chemical conservation laws. This is since $P(\vec{n}^k)$ is conditional on the global state vector (n_1, n_2, \dots, n_N) which is only changed when a chemical reaction occurs (since diffusion cannot cause a global change in the number of molecules but rather only induces a repartitioning of molecules across space).

Now starting from the RDME, we want to calculate the probability $a_j(\vec{n}, \Omega) dt$, in the limit of fast diffusion, that the j th chemical reaction occurs somewhere in the space of volume Ω in the next infinitesimal time interval $[t, t + dt)$, conditional on the global state vector, $\vec{n} = (n_1, n_2, \dots, n_N)$. This reaction can occur in voxel 1, voxel 2, \dots , or voxel M and hence we must sum the propensities of the j th chemical reaction in each voxel. Furthermore, we must also sum over all possible different states in each voxel which are compatible with the global state vector, \vec{n} . Hence it follows that:

$$a_j(\vec{n}, \Omega) = \sum_{k=1}^M \sum_{n_1^k=0}^{n_1} \dots \sum_{n_N^k=0}^{n_N} \hat{a}_j\left(\vec{n}^k, \frac{\Omega}{M}\right) P(\vec{n}^k | \vec{n}). \quad (8)$$

If we use the simplifying assumption that the rate constant of the j th chemical reaction in a voxel is the same as the rate constant of the j th chemical reaction in any other voxel, then in the limit of fast diffusion, the average propensity of the j th chemical reaction in a given voxel is the same as that in any other voxel and hence Eq. (8) further simplifies to:

$$a_j(\vec{n}, \Omega) = M \sum_{n_1^k=0}^{n_1} \dots \sum_{n_N^k=0}^{n_N} \hat{a}_j\left(\vec{n}^k, \frac{\Omega}{M}\right) P(\vec{n}^k | \vec{n}), \quad (9)$$

for some $k = 1, \dots, M$. This can be written conveniently as an expected value under the Binomial distribution defined by Eq. (7):

$$a_j(\vec{n}, \Omega) = M \mathbb{E} \left[\hat{a}_j\left(\vec{n}^k, \frac{\Omega}{M}\right) \right]. \quad (10)$$

By the definition of the propensity function $a_j(\vec{n}, \Omega)$, it follows immediately from the laws of probability that the master equation to which the RDME converges to, in the limit of fast diffusion, is

$$\frac{d}{dt} P(\vec{n}, t) = \sum_{j=1}^R \left(\prod_{i=1}^N E_i^{s_{ij} - r_{ij}} - 1 \right) a_j(\vec{n}, \Omega) P(\vec{n}, t). \quad (11)$$

Note that this equation is identical to Eq. (2) except that \hat{a}_j is replaced with a_j . The main result follows: *The RDME converges to the CME in the limit of fast diffusion if $a_j(\vec{n}, \Omega) = \hat{a}_j(\vec{n}, \Omega)$ for all $j = 1, \dots, R$ (note that this limit is taken with the volume Ω and all rate constants held constant).*

With this in mind, we can define a class of propensities which we call *convergent propensities*. A propensity function $\hat{a}_j(\vec{n}, \Omega)$ is convergent if $a_j(\vec{n}, \Omega) = \hat{a}_j(\vec{n}, \Omega)$. A system consisting exclusively of convergent propensities will have the satisfying property of convergence of the RDME to the CME in the fast diffusion limit. A system with at least one nonconvergent propensity will almost surely not have this property, though this cannot be generally excluded.

D. The RDME and the CME in the limits of fast diffusion and large volumes

We now briefly show that a nonconvergent RDME can still converge to the correct CME in the limit of fast diffusion, if we also take the macroscopic limit of large volumes. The proof is based on the fact that, in the macroscopic limit, the solution of a master equation is increasingly well approximated by the

chemical Langevin equation whose solution has sharp peaks centered on the solution of the corresponding deterministic rate equations (REs) [11].

The REs of system (1) described stochastically by the CME are given by the equation:

$$\frac{d}{dt} \vec{\phi} = \sum_{j=1}^R (r_{ij} - s_{ij}) f_j(\vec{\phi}), \quad (12)$$

where $\vec{\phi} = \langle \vec{n} \rangle / \Omega$ is the vector of deterministic concentrations of species X_1, \dots, X_N (the angled brackets signify the average taken in the macroscopic limit), and $f_j(\vec{\phi})$ is the *macroscopic propensity function* of reaction j defined as:

$$f_j(\vec{\phi}) = \lim_{\Omega \rightarrow \infty} \frac{\hat{a}_j(\vec{n} = \Omega \vec{\phi}, \Omega)}{\Omega}. \quad (13)$$

The REs of the system given by Eqs. (3) and (4), described stochastically by the RDME, are given by:

$$\frac{d}{dt} \phi_i^k = \sum_{j=1}^R (r_{ij} - s_{ij}) f_j(\vec{\phi}^k) + D_i \left(\sum_{k'} \phi_i^{k'} - z \phi_i^k \right), \quad (14)$$

where $\vec{\phi}^k = \langle \vec{n}^k \rangle / (\Omega/M)$ is the vector of deterministic concentrations in voxel k and f_j is the same f_j as defined in Eq. (13). Note that the sum over k' is a sum over the set of voxels neighboring k , and z is the number of neighbours of a voxel for a particular RDME lattice. Clearly, in the limit of fast diffusion, the deterministic concentration of each species is the same in all voxels, i.e., $\phi_i^k = \phi_i^{k'}$ at all times. Hence, the second term on the right-hand side of Eq. (14) equals zero and the rate equations of the RDME simplify to:

$$\frac{d}{dt} \phi_i^k = \sum_{j=1}^R (r_{ij} - s_{ij}) f_j(\vec{\phi}^k). \quad (15)$$

Now to compare with the REs of the CME, we need to use Eq. (15) to derive the REs for the global concentration ϕ_i , which follows from the definition of the global molecule numbers and is given by $\phi_i = \frac{1}{M} (\phi_i^1 + \dots + \phi_i^M)$. These are given by:

$$\begin{aligned} \frac{d}{dt} \phi_i &= \frac{1}{M} \frac{d}{dt} \sum_{k=1}^M \phi_i^k = \frac{1}{M} \sum_{k=1}^M \sum_{j=1}^R (r_{ij} - s_{ij}) f_j(\vec{\phi}^k) \\ &= \sum_{j=1}^R (r_{ij} - s_{ij}) f_j(\vec{\phi}), \end{aligned} \quad (16)$$

where the last equation follows from the fact that in the fast diffusion limit, $\phi_i^k = \phi_i$ at all times. The RE of the global concentrations of the RDME given by Eq. (16) is therefore equal to Eq. (12), the RE of the global concentrations of the CME. In summary, *in the combined limits of fast diffusion and large volumes, the RDME of a system converges to the CME of the same system, regardless of whether the propensities are convergent.*

It can also be straightforwardly shown using the linear noise approximation (LNA) that for deterministically monostable systems, the solution of the RDME and CME, in the macroscopic and fast diffusion limits, tends to the same Gaussian centered on the RE solution [12]. This follows from the fact

that the variance and covariance of the Gaussian are functions of the RE solution, which, as we have shown, is one and the same for the RDME and CME.

III. EXAMPLES OF CONVERGENT AND NONCONVERGENT PROPENSITIES

In this section we test whether some commonly used propensities are in the convergent or nonconvergent class. We shall assume, for simplicity, that the rate constant of the j th chemical reaction in a voxel is the same as the rate constant of the j th chemical reaction in any other voxel.

A. Convergent propensities

Consider mass-action kinetics. It then follows [12] that the propensity of the j th chemical reaction in the CME and of the j th chemical reaction in voxel k of the RDME are respectively given by:

$$\hat{a}_j(\vec{n}, \Omega) = \Omega k_j \prod_{z=1}^N \Omega^{-s_{zj}} \frac{n_z!}{(n_z - s_{zj})!}, \quad (17)$$

$$\hat{a}_j\left(\vec{n}^k, \frac{\Omega}{M}\right) = \frac{\Omega}{M} k_j \prod_{z=1}^N \left(\frac{\Omega}{M}\right)^{-s_{zj}} \frac{n_z^k!}{(n_z^k - s_{zj})!}. \quad (18)$$

The most commonly used types of reactions following mass-action kinetics are the zero-order reaction, first-order reaction, second-order reactions between similar reactants, and second-order reaction with different reactants which have CME propensities $\hat{a}_j(\vec{n}, \Omega)$ equal to $k_j \Omega$, $k_j n_i$, $(k_j/\Omega)n_i(n_i - 1)$, and $(k_j/\Omega)n_i n_j$, respectively, for some integers i and j .

Substituting Eq. (18) in Eq. (9), we have that, in the fast diffusion limit, the RDME converges to a master equation with a propensity for the j th chemical reaction equal to:

$$a_j(\vec{n}, \Omega) = M \prod_{z=1}^N \sum_{n_z^k=0}^{n_z} \hat{a}_j\left(\vec{n}^k, \frac{\Omega}{M}\right) P(n_z^k | n_z), \quad (19)$$

$$= M \frac{\Omega}{M} k_j \prod_{z=1}^N \left(\frac{\Omega}{M}\right)^{-s_{zj}} \sum_{n_z^k=0}^{n_z} \frac{n_z^k!}{(n_z^k - s_{zj})!} P(n_z^k | n_z). \quad (20)$$

$$a_j(\vec{n}, \Omega) = M k_j \sum_{n_i^k=0}^{n_i} \frac{n_i^k}{K + M n_i^k / \Omega} P(n_i^k | n_i),$$

$$= \frac{k_j \Omega (M-1)^{n_i-1} n_i {}_2F_1(K\Omega/M + 1, 1 - n_i; K\Omega/M + 2; -1/(M-1))}{M^{n_i} (K\Omega/M + 1)} \neq \frac{k_j n_i}{K + n_i / \Omega} = \hat{a}_j(\vec{n}, \Omega), \quad (24)$$

where ${}_2F_1(a, b; c; d)$ is a hypergeometric function. Since $a_j(\vec{n}, \Omega) \neq \hat{a}_j(\vec{n}, \Omega)$, it follows that Michaelis-Menten propensities are nonconvergent. However, note in the limits of small n_i^k and of very large n_i^k , that $\hat{a}_j(\vec{n}^k, \frac{\Omega}{M})$ reduces to $k_j n_i^k / K$ and $k_j \Omega / M$, respectively; these are special cases of mass-action kinetics [Eq. (18)] and hence, in these limits,

Now the quantity:

$$\sum_{n_z^k=0}^{n_z} \frac{n_z^k!}{(n_z^k - s_{zj})!} P(n_z^k | n_z), \quad (21)$$

is by definition the s_{zj} -th factorial moment of the binomial distribution $P(n_z^k | n_z)$ with success probability $1/M$ and number of trials n_z . This factorial moment is a standard result (see, for example, Ref. [13]) and is given by:

$$\sum_{n_z^k=0}^{n_z} \frac{n_z^k!}{(n_z^k - s_{zj})!} P(n_z^k | n_z) = \frac{n_z!}{(n_z - s_{zj})!} \left(\frac{1}{M}\right)^{s_{zj}}. \quad (22)$$

Substituting the above equation into Eq. (20) we obtain:

$$a_j(\vec{n}, \Omega) = \Omega k_j \prod_{z=1}^N \Omega^{-s_{zj}} \frac{n_z!}{(n_z - s_{zj})!} = \hat{a}_j(\vec{n}, \Omega). \quad (23)$$

It follows that the propensities of reactions following mass action are convergent; this applies to all reaction orders. The convergence of the RDME to the CME in the fast diffusion limit, for reactions up to second order, has been previously also shown by Gardiner [14] using a completely different method.

B. Nonconvergent propensities

It is common practice to use effective propensities which lump a number of elementary reactions together. One of the most popular such propensities is the Michaelis-Menten propensity. This can model various processes such as nonlinear degradation of a protein, enzyme catalysis of a protein into a product, or the activation of a gene by a protein. Let this protein species be X_i . If the j th reaction is of the Michaelis-Menten type, then it can be described by a term in the deterministic rate equations of the form $f_j(\vec{\phi}) = \frac{k_j \phi_i}{K + \phi_i}$. Using Eq. (13), one can deduce that a corresponding effective propensity in the CME would be $\hat{a}_j(\vec{n}, \Omega) = \frac{k_j n_i}{K + n_i / \Omega}$ [15, 16]. The corresponding propensity in the k th voxel of the RDME would be $\hat{a}_j(\vec{n}^k, \frac{\Omega}{M}) = \frac{k_j n_i^k}{K + M n_i^k / \Omega}$ [17].

Substituting the latter propensity of the RDME in Eq. (9), we have that, in the fast diffusion limit, the RDME converges to a master equation with a propensity for the j th chemical reaction equal to:

the Michaelis-Menten propensity can be considered convergent. The largest deviations from mass action occur when n_i^k / Ω is roughly equal to the constant K (the Michaelis-Menten constant); this is the case where the nonconvergence of the Michaelis-Menten propensity becomes most apparent.

A generalization of the Michaelis-Menten propensity, which is sometimes used, is given by the Hill propensity. For the CME this is given by $\hat{a}_j(\vec{n}, \Omega) = \frac{\Omega k_j (n_i)^\theta}{(\Omega K/M)^\theta + (n_i)^\theta}$, for some i . The Hill coefficient θ is an integer greater than or equal to 1. The corresponding propensity in voxel k of the RDME is $\hat{a}_j(\vec{n}^k, \frac{\Omega}{M}) = \frac{(\Omega/M) k_j (n_i^k)^\theta}{(\Omega K/M)^\theta + (n_i^k)^\theta}$. For general θ it is not possible to evaluate Eq. (9) analytically. However, if we can find a set of parameters for which a_j and \hat{a}_j do not agree, then we can be certain that they are not the same function. Choose, for instance, $k_1 = K = \Omega = 1$, $M = n_i = 2$. For these parameters, $\hat{a}_j = \frac{2^\theta}{1+2^\theta}$. On the other hand, $a_j = \frac{1}{2} [\frac{1}{2} + \frac{1}{(1/2)^\theta + 1} + \frac{1}{2} \frac{2^\theta}{(1/2)^\theta + 2^\theta}]$. There are no real values of θ for which $\hat{a}_j = a_j$, and therefore it follows that Hill-type propensities are nonconvergent.

Another type of propensity related to the ones described above is that used to effectively model the repression of a gene by a protein X_i . In the CME, this propensity is given by $\hat{a}_j(\vec{n}, \Omega) = k_j \Omega \frac{(K \Omega)^\theta}{(K \Omega)^\theta + n_i^\theta}$ [15]. Writing down the RDME equivalent of this propensity and using Eq. (9), one can also show that this propensity is nonconvergent.

IV. SIMPLE CONVERGENT AND NONCONVERGENT EXAMPLE SYSTEMS

To illustrate the results of this paper, we briefly apply them to some simple example systems in this section. For simplicity, we will use systems consisting of only one species.

A. A convergent example

A simple convergent example is given by the open dimerization reaction:



The propensity functions of the CME are

$$\hat{a}_1(n, \Omega) = k_1 \Omega, \hat{a}_2(n, \Omega) = \frac{k_2}{\Omega} n(n-1), \quad (26)$$

where n is the number of X molecules. The corresponding propensity functions in voxel k of the RDME are obtained by replacing n by n^k and Ω by Ω/M . These propensity functions can be nondimensionalized by dividing by $k_1 \Omega$. Then we will have dimensionless propensities:

$$\hat{a}_1 = 1, \hat{a}_2 = K n(n-1), \quad (27)$$

where $K = \frac{k_2}{k_1 \Omega^2}$ is a dimensionless parameter. In the RDME description, the diffusion rate parameter D will be replaced by a dimensionless parameter $D_0 = \frac{D}{k_1 \Omega}$, and the RDME propensities in voxel k will be

$$a_1 = \frac{1}{M}, a_2 = K M n^k (n^k - 1), \quad (28)$$

By the results of Sec. III A, since both propensities are of the mass-action type, they are convergent. Note that the convergence here is obtained in the limit of large D at constant values of the volume and of the rate constants, i.e., the limit that D_0 tends to infinity at constant K . In Fig. 1 we show that the steady-state distribution of global molecule numbers (sum of molecule number over all voxels) calculated using the RDME

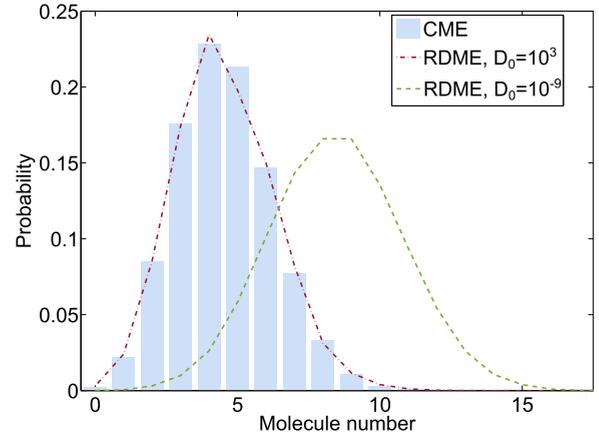


FIG. 1. Steady-state solution of the CME for system (25) (blue histogram) compared with the steady-state solutions of the global molecule numbers calculated using the RDME for very slow diffusion (green dashed line) and for very fast diffusion (red dash-dotted line), all obtained with the SSA. Note that the RDME converges to the CME in the limit of fast diffusion, as predicted by our theory. The parameter values are $K = 0.03$, $M = 10$. Note that D_0 is varied through D while all other parameters are constant.

with very slow diffusion ($D_0 = 10^{-9}$) disagrees with the CME while the same computed with very fast diffusion ($D_0 = 10^3$) agrees exactly with the CME. The plots are obtained using the stochastic simulation algorithm (SSA) for both the CME [18] and RDME [19]. For the RDME, the simulation consisted of 10 voxels connected in a line with reflecting boundaries. The agreement of the CME and RDME in the limit of fast diffusion is in agreement with the theoretical result that both propensities are convergent. Note that the change in the mode of the distribution occurs because the bimolecular reaction happens more frequently when diffusion is fast, thereby reducing the overall molecule number.

B. A nonconvergent example

A simple nonconvergent example is given by a protein production and nonlinear protein degradation system:



The propensity functions in the CME are

$$\hat{a}_1(n, \Omega) = k_1 \Omega, \hat{a}_2(n, \Omega) = \frac{k_2 n}{K + n/\Omega}. \quad (30)$$

The corresponding propensity functions in voxel k of the RDME are obtained by replacing n by n^k and Ω by Ω/M . These propensity functions can be nondimensionalized by dividing by $k_1 \Omega$. Then we will have dimensionless propensities:

$$\hat{a}_1 = 1, \hat{a}_2 = \frac{K_1 n}{K_2 + n}, \quad (31)$$

where $K_1 = \frac{k_2}{k_1}$ and $K_2 = K \Omega$ are dimensionless parameters. In the RDME description, the diffusion rate parameter D will be replaced by a dimensionless parameter $D_0 = \frac{D}{k_1 \Omega}$, and the

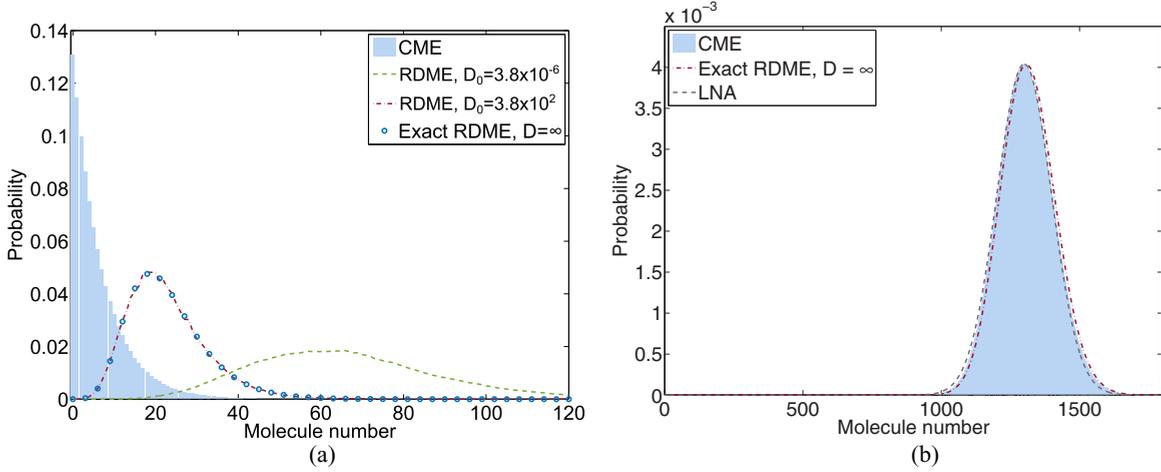


FIG. 2. (a) Steady-state solution of the CME for system (29) (blue histogram) compared with the RDME solutions for slow diffusion (green dashed line) and for fast diffusion (red dash-dotted line), all obtained with the SSA, and the exact RDME solution for infinite diffusion given by Eq. (34) (blue circles). (b) Steady-state exact solution of the CME given by Eq. (33) compared with the steady-state exact solution of the RDME for infinite diffusion given by Eq. (34) and the LNA for system (29). Parameter values are $K_1 = 1.15$, $M = 10$. The nondimensional volume is $K_2 = 0.01$ in (a) and $K_2 = 200$ in (b). D_0 is varied through the diffusion rate D . Note that while the RDME does not agree with the CME in the fast diffusion limit for small volumes (a), it does agree with the CME for fast diffusion in large-enough volumes (b).

RDME propensities in voxel k will be

$$a_1 = \frac{1}{M}, a_2 = \frac{K_1 n^k}{K_2 + M n^k}. \quad (32)$$

By the results of Secs. III A and III B, we see that the first propensity is convergent but the second is not. Note that the convergence of the first propensity here is obtained in the limit of large D at constant values of the volume and of the rate constants, i.e., the limit that D_0 tends to infinity at constant K_1 and K_2 . It follows that the RDME will not

converge to the CME in the fast diffusion limit. In particular, using the method derived in Ref. [20] for general one variable, one-step processes, one can show that the exact steady-state analytical solutions of the CME [Eq. (2) with the propensities given by Eq. (30)] and of the master equation to which the RDME converges in the fast diffusion limit [Eq. (11) with $a_1(n, \Omega) = k_1 \Omega$ and $a_2(n, \Omega)$ given by Eq. (24)] are given by:

$$P(0) = C_1, P(n) = C_1 \prod_{i=1}^n \frac{K_2 + i}{K_1 i} \quad (33)$$

and

$$P(0) = C_2, P(n) = C_2 \prod_{i=1}^n \frac{M^i (K_2/M + 1)}{K_1 (M-1)^{i-1} i {}_2F_1(K_2/M + 1, 1-i; K_2/M + 2; -1/(M-1))}, \quad (34)$$

respectively, where C_1 and C_2 are normalization constants.

In Fig. 2(a) we verify using the SSA that for a small volume ($K_2 = 0.01$) the RDME disagrees with the CME for both very slow and very fast diffusion, i.e., the RDME does not converge to the CME in limit of fast diffusion. Note also that the exact solution of the master equation to which the RDME converges in the fast diffusion limit as given by Eq. (34) agrees very well with that obtained using stochastic simulations of the RDME for large diffusion $D_0 = 3.8 \times 10^2$; this agreement is an independent verification of our theory.

In Fig. 2(b) we show that for large volumes ($K_2 = 200$) the stochastic simulations agree very well with the exact RDME solution Eq. (34) at $D_0 = \infty$ and with the exact CME solution Eq. (33). In this case, the RDME and CME are the Gaussian distribution centered on the solution of the rate equations which is predicted by the LNA. This is in agreement with the results of Sec. II D and shows that the nonconvergence

problems of the RDME are mostly relevant at small volumes (or, equivalently, small molecule numbers).

The nonconvergence shown in this section makes intuitive sense, since the Michaelis-Menten propensity effectively models the enzyme-catalyzed degradation of a protein, assuming that the enzyme and protein substrate in each voxel are in quasiequilibrium which necessarily requires that the diffusion between neighboring voxels is sufficiently slow. This point is also discussed in Ref. [17]. Note, however, that our nonconvergence results apply to any nonelementary propensity, not just those of the Michaelis-Menten type.

V. DISCUSSION

In this paper we have proved a remarkable and counter-intuitive fact, namely that the RDME does not necessarily converge to the CME in the limit of fast diffusion. Conversely, in the limit of *slow* diffusion the RDME decomposes into

a set of noncommunicating voxels with a CME description in each voxel: The RDME will then be accurate, provided that the voxel sizes are sufficiently small that they can be assumed to be well mixed. The RDME with nonelementary reactions can therefore be considered accurate for slow diffusion (and small voxel sizes) and inaccurate for fast diffusion. We can interpret this as implying that the error of the RDME increases as diffusion rates increase. Intuitively, this occurs because nonelementary systems typically arise from assuming that the fastest time scale is a reaction time scale, an assumption which we violate by increasing the diffusion coefficient.

Consequences of this fact for mathematical modeling of biology are numerous. The class of nonconvergent propensities includes Michaelis-Menten-type rates, which are frequently used to model metabolic systems, and Hill-type rates, which describe transcription factor binding. The results of this paper suggest that the RDME cannot be a consistently accurate spatial model of genetic or metabolic networks, unless they

are modelled in complete detail (with all elementary reactions, which is often impossible). For the case when the nonelementary reactions are known to effectively model a system of elementary reactions under quasiequilibrium conditions in well-mixed conditions, the RDME is valid if it can be ascertained that the diffusion is slow enough such that one has chemical quasiequilibrium in each voxel.

Future work in this area may aim at fixing the nonconvergence problem. A particularly interesting idea would be to derive a set of special propensity functions for the RDME which converge to the CME propensities in the limit of fast diffusion. This would ensure a consistent way of performing spatial and stochastic simulations.

ACKNOWLEDGMENTS

This work was supported by a BBSRC EASTBIO Ph.D. studentship to S.S. and by a Leverhulme grant award to R.G. (RPG-2013-171).

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