Chemical Continuous Time Random Walks

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Kinetic Monte Carlo methods such as the Gillespie algorithm model chemical reactions as random walks in particle number space. The interreaction times are exponentially distributed under the assumption that the system is well mixed. We introduce an arbitrary interreaction time distribution, which may account for the impact of incomplete mixing on chemical reactions, and in general stochastic reaction delay, which may represent the impact of extrinsic noise. This process defines an inhomogeneous continuous time random walk in particle number space, from which we derive a generalized chemical master equation. This leads naturally to a generalization of the Gillespie algorithm. Based on this formalism, we determine the modified chemical rate laws for different interreaction time distributions. This framework traces Michaelis–Menten-type kinetics back to finite-mean delay times, and predicts time-nonlocal macroscopic reaction kinetics as a consequence of broadly distributed delays. Non-Markovian kinetics exhibit weak ergodicity breaking and show key features of reactions under local nonequilibrium.

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Chemical reactions are the result of the interaction between different system components. Classically, it is assumed that, within a given support volume, reactants are well mixed. In other words, all reactants are equally available to react at a constant rate. In this case, interreaction times due to intrinsic stochastic variability can be shown to be exponentially distributed [1,2]. These observations form the basis of kinetic Monte Carlo (KMC) methods, such as the Gillespie algorithm [2], which comprise an important class of models and techniques for the stochastic simulation of reactive systems and population dynamics in general [3,4]. The probability distribution of chemical species numbers follows Markovian dynamics in time, which are described by the classical chemical master equation. The corresponding macroscopic dynamics are the familiar local rate laws for species concentrations [5,6]. Since chemical reactions are essentially contact processes leading to nonlinear dynamics, this type of framework finds broad application in population dynamics, modeling scenarios as varied as biological cellular processes, disease spread in epidemiology, dynamics on and of networks, animal species interactions in ecology, quantum molecular dynamics, and chemical reactions in geological media [7–13].

Complex dynamics in heterogeneous environments may manifest themselves in terms of effective, distributed delay times affecting the reaction processes. Transport processes are often at the core of non-Poissonian reaction dynamics, since they are the limiting factor on reactant mixing [14–17]. Medium heterogeneity may affect the efficiency of tracer particles in exploring their surroundings [18–21], thus leading to broad distributions of interreaction times or reaction rate constants [22]. Furthermore, the nonlinear character of reactions may lead to the amplification of local concentration fluctuations, enhancing the effects of transport limitations and significantly slowing down reactions [23]. Heterogeneity and fluctuation processes not inherent to the chemical reaction itself are referred to as extrinsic noise. Modeling the impact of extrinsic noise on chemical reactions in the KMC sense requires a framework capable of representing more complex interreaction times, which describe, for example, transport-induced delays or unresolved reaction sequences [24–28].

The classical chemical master equation rests on two pillars: Exponential waiting times between reactions, and statistical equivalence of all particles of a given species. The present work removes the first assumption and, thereby, implicitly relaxes the second, providing a unified theoretical framework to quantify the impact of arbitrary interreaction times. The continuous time random walk (CTRW) provides a systematic starting point to account for general waiting time distributions between reaction events [29–33]. Building from CTRW theory, we derive a generalized chemical master equation capable of accounting for nonexponential interreaction times and the resulting non-Markovian character of reaction dynamics in time. In the KMC spirit, the dynamics are represented in terms of a random walk in particle number space rather than in physical space. To the best of our knowledge, this Letter provides the first instance of a generalized chemical master equation for a KMC framework that does not assume Markovian (i.e., exponential) waiting times. This allows us to rigorously describe the effects of intrinsic and extrinsic variability of the waiting times and make corresponding predictions about the large-scale behavior. Our approach derives Michaelis–Menten-type kinetics as a result of random delay times with a finite mean and predicts time-nonlocal macroscopic reaction kinetics as a consequence of broadly distributed delays. The latter show weak ergodicity breaking, a fingerprint of anomalous transport [34–39], and exhibit key features of local non-equilibrium such as power law mass decay.

Framework.—In order to cast the dynamics of m_s different species that participate in m_r different reactions into a CTRW framework, we first define the state space. The chemical species are denoted by $\mathcal{S}_j$, where $j = 1, \ldots, m_s$; the corresponding particle numbers are denoted by n_j. The state vector of particle numbers is $\boldsymbol{n} = (n_1, \ldots, n_{m_s})^\top$, where the superscript $\top$ denotes the transpose. During a reaction i the loss (gain) in particle number n_j is denoted by $r_{ij} \in \mathbb{N}$ ($p_{ij} \in \mathbb{N}$). These coefficients are typically, but need not be, given by the law of mass action. Thus, the impact of reaction i on the state space can be expressed as

$$\sum_j r_{ij}\mathcal{S}_j \to \sum_j p_{ij}\mathcal{S}_j. \tag{1}$$

The stoichiometric coefficients $s_{ij} = p_{ij} - r_{ij}$ denote the net change in each species j due to each reaction i. A single event of reaction i is characterized by the reaction waiting time $\tau_{(i)}^r$ whose probability density function (PDF) ψ_i^r depends, in general, on the system state $\boldsymbol{n}$; we will elaborate on its specific form below. The reaction event that actually occurs is the one whose waiting time is minimum. Thus, the waiting time between reaction events is $\tau^r = \min(\tau_{(i)}^r | i = 1, \ldots, m_r)$. The joint distribution $\phi_i^r(t;\boldsymbol{n})dt$ of reaction i happening and the reaction waiting time being in $[t, t + dt]$ is then given by [40]

$$\phi_i^r(t;\boldsymbol{n}) = \psi_i^r(t;\boldsymbol{n})\prod_{\ell\neq i}\int_t^\infty dt_\ell \psi_\ell^r(t_\ell;\boldsymbol{n}), \tag{2}$$

which states that $\phi_i^r(t;\boldsymbol{n})$ is given by the probability that the reaction times of the $\ell \neq i$ reactions are larger than the one for reaction i, multiplied by the PDF of the waiting time of reaction i, ψ_i^r.

For the modeling of system fluctuations in terms of waiting times, we distinguish between intrinsic and extrinsic noise. Extrinsic noise results from external fluctuations, that is, variability in the physical or chemical environment. Under transport-limited conditions, reaction delays arise from mass transfer limitations due to reactants' spatial sampling efficiency and fluctuation-induced segregation [17,23]. In the KMC spirit, these delays affect all particles in the same way independently of the system state. This is in contrast to intrinsic noise, which, by definition, represents the inherent stochasticity of the reaction process proper [6,25,42]. Thus, we introduce a global delay time τ^g such that, for a given state $\boldsymbol{n}$, the interreaction time is $\tau = \tau^r(\boldsymbol{n}) + \tau^g(\tau^r)$. The global delay does not depend directly on the state, but may depend on the current reaction waiting time τ^r. As mentioned above, τ^g is a manifestation of extrinsic noise, and the reaction waiting times τ^r of intrinsic noise. The joint distribution for reaction i to happen after an interreaction time in $[t, t + dt]$ is denoted by $\phi_i(t,\boldsymbol{n})dt$. We consider two global delay scenarios. Scenario 1 assumes that τ^g is independent of the reaction-specific waiting times and identically distributed, with density ψ^g. In this case, we have $\phi_i(t;\boldsymbol{n}) = (\phi_i^r * \psi^g)(t;\boldsymbol{n})$, where $*$ denotes convolution. Scenario 2 considers τ^g to be given by a compound Poisson process as $\tau^g(\tau^r) = \sum_{k=1}^{\eta(\tau^r)} \vartheta_k^g$, where $\eta(u)$ is Poisson-distributed with mean γu; the density of the identical independently distributed ϑ_k^g is denoted by ψ_0^g. The joint distribution $\phi_i(t;\boldsymbol{n})$ can be expressed in Laplace space as $\tilde{\phi}_i(\lambda;\boldsymbol{n}) = \tilde{\phi}_i^r(\lambda + \gamma[1 - \tilde{\psi}_0^g(\lambda)];\boldsymbol{n})$ [43,44]. Laplace transformed quantities are denoted by a tilde, and the Laplace variable is denoted by λ. Both scenarios represent global delays of the full reaction system. In scenario 1, the delay is synchronized with the reaction events themselves. The delay time can be seen as a global "preparation" time for the next reaction event. This means the delay time is external, but the delay event is triggered by the reaction event. In scenario 2, both delay time and occurrence of delay events (characterized by the rate γ) are prescribed externally. Such fixed-rate delay events can be related to fluctuation-induced spatial segregation [45].

The CTRW dynamics for the stochastic process describing the random particle number vector $\boldsymbol{N}_k$ and time T_k after k reaction steps can now be defined by the recursion relations

$$\boldsymbol{N}_{k+1} = \boldsymbol{N}_k + \boldsymbol{s}_{r_k}, \qquad T_{k+1} = T_k + \tau_k, \tag{3}$$

where $\boldsymbol{s}_{r_k} = (s_{r_k 1}, \ldots, s_{r_k m_s})^\top$ and the random number $r_k \in (1, \ldots, m_r)$ indicates the reaction that is occurring. The joint distribution of (r_k, τ_k) is given by $\phi_i(t;\boldsymbol{n})$. The initial conditions are deterministic, $\boldsymbol{N}_0 = \boldsymbol{n}_0$ and $T_0 = 0$. The recursion relations (3) define an inhomogeneous multidimensional CTRW because the joint distribution of (r_k, τ_k) depends on the current system state $\boldsymbol{N}_k$. We use the CTRW formalism [46] to derive the following generalized chemical master equation for the probability $P(\boldsymbol{n}, t)$ of finding the system in state $\boldsymbol{n}$ at time t [40]:

$$\partial_t P(\boldsymbol{n}, t) = \sum_i \int_0^t dt' \left(\prod_j \mathbb{E}_j^{-s_{ij}} - 1\right) P(\boldsymbol{n}, t') M_i(t - t';\boldsymbol{n}), \tag{4}$$

where the step operator $\mathbb{E}_j^z$ acts on a function $f(\boldsymbol{n})$ by incrementing the particle number n_j of species $\mathcal{S}_j$ by the integer $z \in \mathbb{Z}$, i.e., $\mathbb{E}_j^z f(\boldsymbol{n}) = f(n_1, \ldots, n_j + z, \ldots, n_{m_s})$ [6]. The memory functions M_i are defined by their Laplace transforms as [40]

$$\tilde{M}_i(\lambda;\boldsymbol{n}) = \frac{\lambda\tilde{\phi}_i(\lambda;\boldsymbol{n})}{1-\sum_\ell \tilde{\phi}_\ell(\lambda;\boldsymbol{n})}, \tag{5}$$

whose form is typical of the CTRW key formalism [46]. Note that (4) describes the full evolution of the nonlinear dynamic system (3), in which the random increments depend on the system state. The generalized chemical master equation is inhomogeneous in that the memory function depends explicitly on the state vector $\boldsymbol{n}$. It generalizes the chemical master equation [2,5]. A generalized Gillespie algorithm corresponding to (4) is described in [40].

Chemical rate laws.—In order to characterize the impact of stochastic delay on macroscopic reaction dynamics, we focus on the corresponding rate laws. The dimensionless concentrations are defined by $\boldsymbol{C} = \boldsymbol{N}/n_0$, with $n_0 = \sum_j n_{j,0}$. The macroscopic concentration is given by the ensemble average $\langle \boldsymbol{C} \rangle$. We derive the following macroscopic equations [40]:

$$\partial_t \langle \boldsymbol{C} \rangle = \sum_i \boldsymbol{s}_i \int_0^\infty dt' \langle M_i^C[t-t';\boldsymbol{C}(t')] \rangle, \tag{6}$$

where we define $M_i^C[t;\boldsymbol{C}(t)] = M_i[t;n_0\boldsymbol{C}(t)]/n_0$. Note that these key equations are, in general, not closed. Nontrivial scenarios for which closures of (6) are available, and situations for which they are not, are discussed in the following.

Reaction waiting times.—The waiting time associated with reaction i events is given by the minimum intrinsic reaction time, which is distributed according to a given PDF p_i. Thus, the state-dependent density of waiting times for reaction i is [40]

$$\psi_i^r(t;\boldsymbol{n}) = h_i(\boldsymbol{n}) p_i(t) \left(\int_t^\infty dt' p_i(t') \right)^{h_i(\boldsymbol{n})-1}, \tag{7}$$

where $h_i(\boldsymbol{n}) = \prod_j n_j!/[r_{ij}!(n_j - r_{ij})!]$ accounts for all possible combinations of necessary reactants. Thus, we obtain from (2), for the joint density of reaction i happening with the reaction time t

$$\phi_i^r(t;\boldsymbol{n}) = \frac{h_i(\boldsymbol{n}) p_i(t)}{\int_t^\infty dt' p_i(t')} \prod_{\ell=1}^{m_r} \left(\int_t^\infty dt_\ell \, p_\ell(t_\ell) \right)^{h_\ell(\boldsymbol{n})}. \tag{8}$$

In the following, we briefly discuss the intrinsic reaction waiting time statistics before we analyze, in detail, the impact of reaction delay due to extrinsic noise.

Intrinsic reaction waiting times.—The intrinsic reaction waiting times are a consequence of the intrinsic system noise. In the proposed KMC framework, the intrinsic waiting times are reset after a reaction event. Considering the reaction process as a superposition of renewal processes [47,48], this implies that the time to the next reaction after a certain time has elapsed, that is, the forward recurrence time, has the same distribution as the reaction time itself. This is a property of the exponential distribution only. Thus, in the following, we consider the intrinsic reaction waiting times to be exponentially distributed. For $p_i(t) = \kappa_i e^{-\kappa_i t}$, with κ_i the (microscopic) reaction rate, the joint distribution (8) becomes $\phi_i^r = h_i \kappa_i \exp(-\sum_\ell \kappa_\ell h_\ell t)$. In the absence of delay, that is, for $\phi_i \equiv \phi_i^r$, the memory function is obtained by Laplace inversion of (5) as $M_i = h_i \kappa_i \delta(t)$, where $\delta(\cdot)$ is the Dirac delta. The generalized chemical master equation (4) then becomes the well-known chemical master equation [5], which describes Markovian dynamics. The kinetic rate laws are obtained from (6) by approximating $h_i(\boldsymbol{n}) \approx \prod_j n_j^{r_{ij}}/r_{ij}!$ for large n_j as

$$\partial_t \langle \boldsymbol{C} \rangle = \sum_i \boldsymbol{s}_i \kappa_i^C \prod_j \langle C_j \rangle^{r_{ij}}, \tag{9}$$

where $\langle C_j^{r_{ij}} \rangle \approx \langle C_j \rangle^{r_{ij}}$ for large particle numbers because P becomes strongly peaked about the ensemble average [6]. The (macroscopic) rate constants are given by $\kappa_i^C = n_0^{\alpha_i - 1} \kappa_i / \prod_j r_{ij}!$, where $\alpha_i = \sum_j r_{ij}$ is the order of reaction i. In the following, we focus on the analysis of non-Markovian behaviors due to extrinsic noise as reflected in scenarios 1 and 2.

Global delay: Scenario 1.—First, we consider a finite-mean delay with $\langle \tau^g \rangle = \mu$. For $\lambda \ll \mu^{-1}$, we may write $\tilde{\psi}^g \approx 1 - \mu\lambda$. Thus, we obtain, together with the exponential form of the ϕ_i^r given above, the following approximation for the memory functions at $t \gg \mu$:

$$M_i(t;\boldsymbol{n}) = \frac{\kappa_i h_i(\boldsymbol{n})}{1 + \mu \sum_\ell \kappa_\ell h_\ell(\boldsymbol{n})} \delta(t). \tag{10}$$

The kinetic rate laws obtained from (9) describe generalized Michaelis–Menten kinetics

$$\partial_t \langle \boldsymbol{C} \rangle = \sum_i \boldsymbol{s}_i \frac{\kappa_i^C \prod_j \langle C_j \rangle^{r_{ij}}}{1 + \mu^C \sum_k \kappa_k^C \prod_\ell \langle C_\ell \rangle^{r_{k\ell}}}, \tag{11}$$

where the macroscopic mean global delay $\mu^C = n_0 \mu$. Figure 1 illustrates the results discussed up to here for irreversible second-order reactions $\mathcal{S}_1 + \mathcal{S}_2 \to \varnothing$ with equal initial concentrations c_0 for both species.

Global delay: Scenario 2.—The memory functions for scenario 2 are given by $\tilde{M}_i = \lambda h_i \kappa_i / [\lambda + \gamma(1 - \tilde{\psi}_0^g)]$. We consider a heavy tailed single-event delay PDF $\psi_0^g \sim t^{-1-\beta}$, such that $\tilde{\psi}_0^g(\lambda) \approx 1 - (\mu\lambda)^\beta$ for $\lambda \ll \mu^{-1}$. Here, μ is a characteristic time scale and $0 < \beta < 1$. Note that such a delay is a parsimonious model for infinite-mean random variables due to the generalized central limit theorem [49]. This leads to the approximate memory function $\tilde{M}_i = h_i \kappa_i (t_w \lambda)^{1-\beta}$ for $t \gg t_w$ and $t \gg \mu$ [40], where we defined the effective delay time scale $t_w = (\gamma \mu^\beta)^{-1/(1-\beta)}$. The

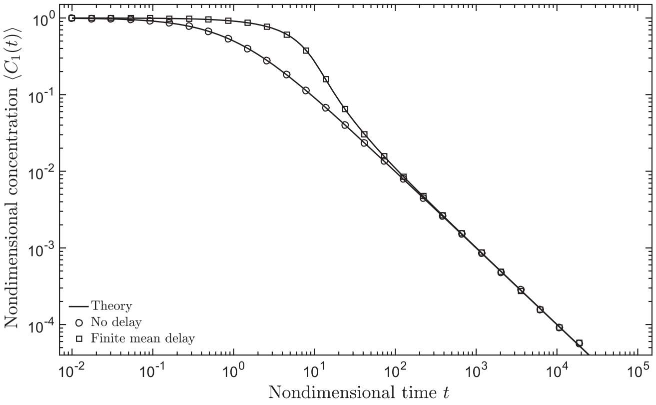

FIG. 1. Mean concentration for two concurrent second order annihilation reactions $\mathcal{S}_1 + \mathcal{S}_2 \to \varnothing$ with exponential intrinsic waiting times, without delay, and with finite-mean global delay (scenario 1). The macroscopic reaction rates are $\kappa_1^C = 0.3$ and $\kappa_2^C = 0.7$, and the macroscopic mean delay is $\mu^C = 10$. Simulations (symbols) are single realizations with $n_0 = 10^6$. Time is nondimensionalized by $t_r = 1/[(\kappa_1^C + \kappa_2^C)c_0]$ and concentration by c_0.

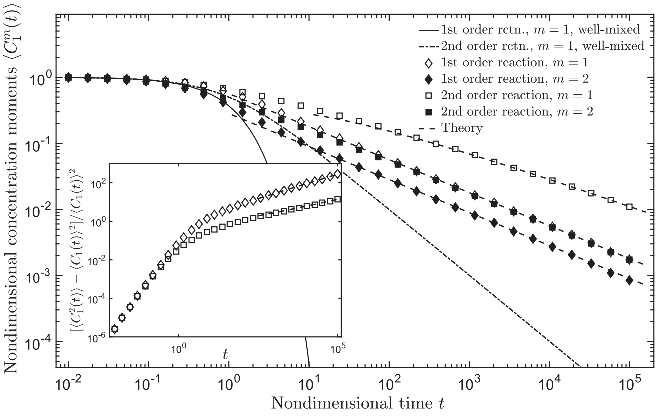

FIG. 2. Moments of concentration for first order $\mathcal{S}_1 \to \varnothing$ and second order $S_1 + \mathcal{S}_2 \to \varnothing$ annihilation reactions with infinite-mean delay (scenario 2). The single-event delay exponent is $\beta = 1/2$, the effective delay time scale is $t_w = 1$, and the rate of delay events is $\gamma = 10^2$. Simulations are averaged over 10^5 realizations with 10^6 particles. Time is nondimensionalized by $t_r = 1/(\kappa^C c_0^{\alpha-1})$ and concentration by c_0. The inset illustrates the breakdown of the $\langle C^2\rangle = \langle C\rangle^2$ closure induced by weak ergodicity breaking.

resulting rate laws are time nonlocal and can be expressed in terms of fractional-in-time evolution equations

$$\partial_t\langle \boldsymbol{C}\rangle = \sum_i \boldsymbol{s}_i \kappa_i^C t_w^{1-\beta}\partial_t^{1-\beta}\left\langle \prod_j C_j^{r_{ij}}\right\rangle. \tag{12}$$

Unlike for the case of finite mean delay, here, $\langle \prod_j C_j^{r_{ij}}\rangle \neq \prod_j \langle C_j\rangle^{r_{ij}}$ in the thermodynamic limit of infinite particle numbers, expressing the impact of local nonequilibrium. The ensemble average concentrations and their moments can be obtained by subordination [49,50] from the solutions of the corresponding well-mixed problem, which satisfy (9) [40]. The behavior in single realizations of the chemical system is different from the ensemble behavior because large delay events with no change in concentration dominate. In this sense, while the intrinsic reaction conditions are the same in each realization, the global reaction behaviors are different, and thus, particles in different realizations are not statistically equivalent. The system is weakly ergodicity breaking [34,35], which is a common characteristic of anomalous transport in heterogeneous environments.

To illustrate these findings, we consider annihilation reactions of order α, $\sum_{i=1}^{\alpha} \mathcal{S}_i \to \varnothing$, with equal initial concentration c_0 for all species. The long time limit of Eq. (12) predicts the asymptotics $\langle C_i^{\alpha}(t)\rangle \propto t^{-\beta}$. For $\alpha = 1$, all concentration moments decay algebraically. The survival probability is dominated by the distribution of reaction delays, and given by the probability that the interreaction time is larger than t. The relative concentration variance $(\langle C_i^2\rangle - \langle C_i\rangle^2)/\langle C_i\rangle^2$ increases as t^{β}. For $\alpha = 2$, a reaction event corresponds to the annihilation of a pair, and this, in turn, is dictated by the delay times. This means that pair survival is governed by the delay time distribution. The mean concentration, on the other hand, behaves asymptotically as $\langle C_i\rangle \propto t^{-\beta}\ln(t)$ [40]. Thus, the relative variance behaves as $t^{\beta}/\ln(t)^2$. This type of behavior is characteristic of concentration fluctuations in random media under anomalous transport [51,52]. Figure 2 shows the evolution of the mean and mean squared concentrations for $\alpha = 1$ and 2.

Conclusions.—We have proposed a CTRW approach for chemical reactions under nonideal conditions which relaxes the fundamental assumptions of classical KMC methods, namely, those of exponential interreaction times and statistical equivalence of all particles. The resulting chemical CTRW is inhomogeneous in that its evolution depends on the system state. This is a direct consequence of the dependence of the reaction waiting times on the particle numbers intrinsic to KMC methods. The global delay approach describes the impact of extrinsic noise on the reaction dynamics. It may not be applicable directly to situations in which the delay is reaction dependent because the chemical CTRW (3) implies that the delay conditions are reset after the reaction fires. The work of [28] provides a framework for dealing with reaction-specific delays, although it requires *ad hoc* identification of different orders of reaction firing. In conclusion, the proposed chemical CTRW provides an approach to account for the impact of ambient fluctuations, which may open new ways of understanding and modeling reaction phenomena under nonideal conditions. It derives generalized Michaelis–Menten kinetics as a result of finite-mean random delay, and time-nonlocal kinetic rate laws for heavy-tailed delay time distributions.

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