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 inter-reaction times are exponentially distributed under the assumption that the system is well mixed. We introduce an arbitrary inter-reaction 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 inter-reaction 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 non-equilibrium.

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, inter-reaction 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 inter-reaction 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 inter-reaction 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 inter-reaction 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 non-exponential inter-reaction 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 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 $\tau^r_{(i)}$ whose probability density function (PDF) ψ^r_i 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 $\tau^r = \min\{\tau^r_{(i)} | i = 1, \ldots, m_r\}$. The joint distribution $\phi^r_i(t; \boldsymbol{n}) \mathrm{d}t$ of reaction i happening and the reaction waiting time being in $[t, t + \mathrm{d}t]$ is then given by (see Appendix A)

$$\phi^r_i(t; \boldsymbol{n}) = \psi^r_i(t; \boldsymbol{n}) \prod_{\ell \neq i} \int_t^\infty \mathrm{d}t_\ell \, \psi^r_\ell(t_\ell; \boldsymbol{n}), \tag{2}$$

which states that $\phi^r_i(t; \boldsymbol{n})$ 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^r_i.

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, 40]. Thus, we introduce a global delay time τ^g such that for a given state $\boldsymbol{n}$ the inter-reaction 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 inter-reaction time in $[t, t + \mathrm{d}t]$ is denoted by $\phi_i(t, \boldsymbol{n}) \mathrm{d}t$. 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 $\phi_i(t; \boldsymbol{n}) =$

$(\phi^r_i * \psi^g)(t; \boldsymbol{n})$, where $*$ denotes convolution. *Scenario 2* considers τ^g to be given by a compound Poisson process as $\tau^g(\tau^r) = \sum_{k=1}^{\eta(\tau^r)} \vartheta^g_k$, where $\eta(u)$ is Poisson-distributed with mean γu; the density of the identical independently distributed ϑ^g_k is denoted by ψ^g_0. The joint distribution $\phi_i(t; \boldsymbol{n})$ can be expressed in Laplace space as $\tilde{\phi}_i(\lambda; \boldsymbol{n}) = \tilde{\phi}^r_i(\lambda + \gamma[1 - \tilde{\psi}^g_0(\lambda)]; \boldsymbol{n})$ [41, 42]. 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 [43].

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 multi-dimensional CTRW because the joint distribution of (r_k, τ_k) depends on the current system state $\boldsymbol{N}_k$. We use the CTRW formalism [44] 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 (see Appendix B),

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

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 (see Appendix B)

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

whose form is typical of the CTRW key formalism [44]. Note that (4) describes the full evolution of the non-linear 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 Appendix D.

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 (see Appendix C),

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

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 (see Appendix A)

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

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 that reaction i happens with the reaction time t

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

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 [45, 46], 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

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

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 – We consider first 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 $t \gg \mu$ (see Appendix E),

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

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

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

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.

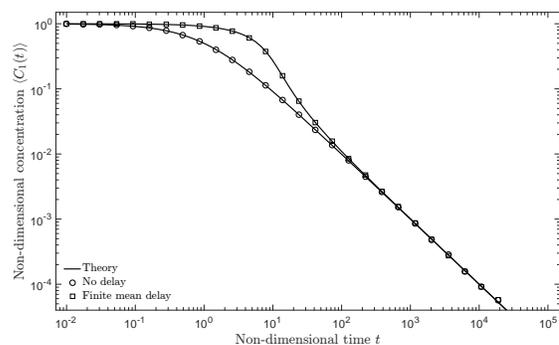Figure 1. Mean concentration for two concurrent second order annihilation reactions $\mathcal{S}_1 + \mathcal{S}_2 \to \varnothing$ with exponential intrinsic waiting times, without delay and with finite-mean global delay (scenario 1). The macroscopic reaction rates are $\kappa_1^C = 0.3$ and $\kappa_2^C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

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 timescale 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 [47]. This leads to the approximate memory function $M_i = h_i \kappa_i (t_w \lambda)^{1-\beta}$ for $t \gg t_w$ and $t \gg \mu$ (see Appendix F), where we defined the effective delay timescale $t_w = (\gamma\mu^\beta)^{-1/(1-\beta)}$. The resulting rate laws are time non-local and can be expressed in terms of fractional-in-time evolution equations,

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

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 non-equilibrium. The ensemble average concentrations and their moments can be obtained by subordination [47, 48] from the solutions of the corresponding well-mixed problem, which satisfy (9), see Appendix F. 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 inter-reaction 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 $\langle C_i \rangle \propto t^{-\beta} \ln(t)$, see Appendix F. Thus, the relative variance behaves as $t^\beta / \ln(t)^2$. This type of behaviors is characteristic of concentration fluctuations in random media under anomalous transport [49, 50]. 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 non-ideal conditions which relaxes the fundamental assumptions of classical KMC methods, namely those of exponential inter-reaction
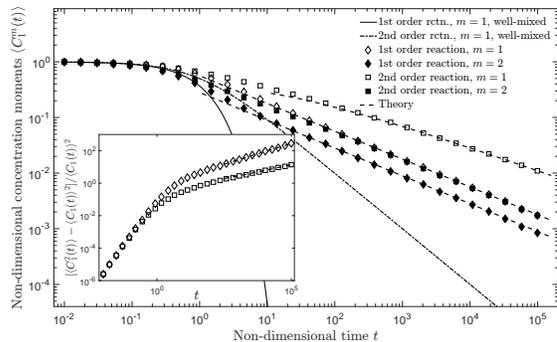

Figure 2. Moments of concentration for first order $\mathcal{S}_1 \to \varnothing$ and second order $\mathcal{S}_1 + \mathcal{S}_2 \to \varnothing$ annihilation reactions with infinite-mean delay (scenario 2). The single-event delay exponent is $\beta = 1/2$, the effective delay timescale is $t_w = 1$, and the rate of delay events is $\gamma = 10^2$. Simulations are averaged over 10^5 realizations with 10^6 particles. Time is non-dimensionalized 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.

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. 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 non-ideal 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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Appendix A: Inter-reaction waiting times

Here we provide some details on the derivation of Eqs. (2), (7) and (8). First, let us address the problem of obtaining the joint density ϕ_i^r for reaction i to occur after the reaction waiting time t, where the single-reaction waiting times are distributed according to ψ_i^r. In this discussion we disregard global delay; its inclusion is discussed in the main text. This inter-reaction waiting time is $\tau^r(\boldsymbol{n})$, given, by definition, by the minimum waiting time to any reaction. Since the state is fixed until the next reaction occurs, we have

$$\tau^r(\boldsymbol{n}) = \min\{\tau_{(i)}^r(\boldsymbol{n}) \mid i = 1, \ldots, m_r\} \,, \tag{A1}$$

where $\tau_{(i)}^r(\boldsymbol{n})$ is the waiting time of reaction i. Thus, ϕ_i^r is given by

$$\begin{aligned}
\phi_i^r(t; \boldsymbol{n}) &= \langle \delta[t - \tau_{(i)}^r(\boldsymbol{n})]\Theta[\min(\tau_{(\ell)}^r | \ell \neq i) - t]\rangle \,, \\
&= \langle \delta[t - \tau_{(i)}^r(\boldsymbol{n})] \prod_{\ell \neq i} \Theta[\tau_{(\ell)}^r(\boldsymbol{n}) - t]\rangle \,,
\end{aligned} \tag{A2}$$

where $\Theta(\cdot)$ is the Heaviside step function. The reaction waiting times $\tau_{(i)}^r$ are mutually independent, and thus

$$\begin{aligned}
\phi_i^r(t; \boldsymbol{n}) &= \int_0^\infty \mathrm{d}t' \, \psi_i^r(t'; \boldsymbol{n})\delta(t - t') \prod_{\ell \neq i} \int_0^\infty \mathrm{d}t_\ell \, \psi_\ell^r(t_\ell; \boldsymbol{n})\Theta(t_\ell - t) \,, \\
&= \psi_i^r(t; \boldsymbol{n}) \prod_{\ell \neq i} \int_t^\infty \mathrm{d}t_\ell \, \psi_\ell^r(t_\ell; \boldsymbol{n}) \,.
\end{aligned} \tag{A3}$$

The expression for the PDF ψ_i^r of reaction waiting times τ_i^r is obtained in the same way. The number of possible reaction events of reaction i is given by $h_i(\boldsymbol{n})$, which counts all possible combinations of particles and thus depends on the state $\boldsymbol{n}$. Each of the possible h_i events is characterized by an intrinsic reaction waiting time θ, which is distributed according to p_i. The reaction waiting time is given by

$$\tau_i^r(\boldsymbol{n}) = \min\{\theta_\ell | \ell = 1, \ldots, h_i(\boldsymbol{n})\} \,. \tag{A4}$$

Its PDF is thus given by

$$\begin{aligned}
\psi_i^r(t; \boldsymbol{n}) &= \langle \delta[t - \min(\theta_\ell | \ell = 1, \ldots, h_i(\boldsymbol{n})]\rangle = \prod_{\ell=1}^{h_i(\boldsymbol{n})} \int_0^\infty \mathrm{d}t_\ell \, p_i(t_\ell)\delta[t - \min\{\theta_\ell\}] \,, \\
&= h_i(\boldsymbol{n})p_i(t) \left[\int_t^\infty \mathrm{d}t' p_i(t')\right]^{h_i - 1} \,.
\end{aligned} \tag{A5}$$

The latter can also be written as

$$\psi_i^r(t; \boldsymbol{n}) = -\partial_t \left[\int_t^\infty \mathrm{d}t' p_i(t')\right]^{h_i(\boldsymbol{n})} \,. \tag{A6}$$

Using (A5) and (A6) in (A3) gives

$$\begin{aligned}
\phi_i^r(t; \boldsymbol{n}) &= h_i(\boldsymbol{n})p_i(t) \left[\int_t^\infty \mathrm{d}t' p_i(t')\right]^{h_i(\boldsymbol{n}) - 1} \prod_{\ell \neq i} \left[\int_t^\infty \mathrm{d}t' p_\ell(t')\right]^{h_\ell(\boldsymbol{n})} \,, \\
&= \frac{h_i(\boldsymbol{n})p_i(t)}{\int_t^\infty \mathrm{d}t' p_i(t')} \prod_{\ell=1}^{m_r} \left[\int_t^\infty \mathrm{d}t' p_\ell(t')\right]^{h_\ell(\boldsymbol{n})} \,.
\end{aligned} \tag{A7}$$

Appendix B: Generalized chemical master equation

The recursion relations

$$\boldsymbol{N}_{k+1} = \boldsymbol{N}_k + \boldsymbol{s}_{r_k} \,, \qquad T_{k+1} = T_k + \tau_k \tag{B1}$$

for the state vector $\boldsymbol{N}_k$ and time T_k describe an inhomogeneous CTRW process. Thus, we now adapt the CTRW formalism in order to derive the corresponding generalized chemical master equation. We now wish to describe the evolution of particle numbers in time t rather than k. Thus, consider the renewal process K_t, which describes the number of steps as a function of time. We write $\boldsymbol{N}(t) = \boldsymbol{N}_{K_t}$. The process K_t is the adjoint of the process T_k, which describes the time elapsed after k reaction steps. We have $T_{K_t} = t$, and $K_t = \sup\{k \mid T_k < t\}$. We can now write for the probability of $\boldsymbol{N}(t) = \boldsymbol{n}$

$$P(\boldsymbol{n}, t) = \langle \delta_{\boldsymbol{n}, \boldsymbol{N}_{K_t}} \rangle \,, \tag{B2}$$

where the angular brackets denote the average over all realizations of the waiting time process τ_k, and $\delta_{i,j}$ is the Kronecker delta. Using a partition of unity, we write

$$P(\boldsymbol{n}, t) = \sum_{k=0}^{\infty} \langle \delta_{\boldsymbol{n}, \boldsymbol{N}_k} \delta_{k, K_t} \rangle \,. \tag{B3}$$

The goal now is to split the average. This can be done by noticing that

$$\delta_{k, K_t} = \mathbb{I}(T_k \leq t < T_{k+1}) \,, \tag{B4}$$

where $\mathbb{I}(\cdot)$ is an indicator function which is 1 if the argument is true and 0 otherwise. Thus, introducing another partition of unity, we obtain

$$P(\boldsymbol{n}, t) = \int_0^{\infty} \mathrm{d}t' \sum_{k=0}^{\infty} \langle \delta_{\boldsymbol{n}, \boldsymbol{N}_k} \delta(T_k - t') \mathbb{I}(0 \leq t - t' < \tau_k) \rangle \,. \tag{B5}$$

Since the waiting times τ_k are independent we obtain

$$P(\boldsymbol{n}, t) = \int_0^t \mathrm{d}t' \sum_{k=0}^{\infty} R_k(\boldsymbol{n}, t') \sum_{i=1}^{m_r} \int_{t-t'}^{\infty} \mathrm{d}t'' \, \phi_i(t''; \boldsymbol{n}) \,, \tag{B6}$$

where

$$R_k(\boldsymbol{n}, t) = \langle \delta_{\boldsymbol{n}, \boldsymbol{N}_k} \delta(T_k - t) \rangle \tag{B7}$$

is the joint density of arriving at $\boldsymbol{n}$ at time t after k reaction steps. It follows that $R(\boldsymbol{n}, t) = \sum_{k=0}^{\infty} R_k(\boldsymbol{n}, t)$ is the probability per time of arriving at $\boldsymbol{n}$ at time t after any number of reaction steps. Thus, Eq. (B6) has a clear physical interpretation: The probability of finding $\boldsymbol{n}$ at time t is given by the probability density of having arrived at an earlier time t', and then not reacting the remaining time $t - t'$, integrated over any arrival time t'. Note that (B1) is a Markov process in reaction step numbers k and $R_k(\boldsymbol{n}, t)$ is its density. Thus, $R_k(\boldsymbol{n}, t)$ fulfills the Chapman-Kolmogorov equation

$$R_{k+1}(\boldsymbol{n}, t) = \int_0^t \mathrm{d}t' \sum_{i=1}^{m_r} R_k(\boldsymbol{n} - \boldsymbol{s}_i, t') \phi_i(t - t'; \boldsymbol{n} - \boldsymbol{s}_i) \,. \tag{B8}$$

Note that $R_0(\boldsymbol{n}, t) = \langle \delta_{\boldsymbol{n}, \boldsymbol{N}_0} \delta(T_0 - t) \rangle = P(\boldsymbol{n}, 0)\delta(t)$, where $T_0 = 0$ was taken as zero without loss of generality. If the initial condition is deterministic, one has also $P(n, 0) = \delta_{n, \boldsymbol{n}_0}$ for some given initial particle numbers $\boldsymbol{n}_0$.

Due to the convolutions, Eqs. (B6) and (B7) form a system that is most easily solved in Laplace space, where we have

$$\tilde{R}(\boldsymbol{n}, \lambda) = P(\boldsymbol{n}, 0) + \sum_{i=1}^{m_r} \tilde{R}(\boldsymbol{n} - \boldsymbol{s}_i, \lambda) \tilde{\phi}_i(\lambda; \boldsymbol{n} - \boldsymbol{s}_i) \,,$$

$$\tilde{P}(\boldsymbol{n}, \lambda) = \tilde{R}(\boldsymbol{n}, \lambda) \frac{1 - \sum_i \tilde{\phi}_i(\lambda; \boldsymbol{n})}{\lambda} \,. \tag{B9}$$

It is possible to solve this system for $\tilde{P}$ through algebraic manipulations alone, giving

$$\lambda \tilde{P}(\boldsymbol{n}, \lambda) = P(\boldsymbol{n}, 0) + \sum_{i=1}^{m_r} \left(\prod_{j=1}^{m_s} \mathbb{E}^{-s_{ij}} - 1 \right) \tilde{P}(\boldsymbol{n}, \lambda) \tilde{M}_i(\lambda; \boldsymbol{n}) , \tag{B10}$$

where $\tilde{M}_i(\lambda; \boldsymbol{n})$ is given by Eq. (5). Recognizing the products $\tilde{P}\tilde{M}_i$ as corresponding to convolutions in the time domain, Laplace inversion leads directly to the generalized master equation (4).

Appendix C: Chemical rate laws

The generalized chemical master equation (4) is exact, i.e., it involves no approximations given our conceptualization of the problem. However, it is sometimes convenient to describe the macroscopic behavior of a system directly. Specifically, the (ensemble) average concentration is often a quantity of interest, and may be described by a simpler, ordinary (integro-)differential equation rather than the full master equation. We thus develop here an equation for the first ensemble moment of the probability distribution of particle numbers P, valid at large particle numbers.

First, the step operators in Eq. (4) may be approximated by derivatives in the following way. Using the definition of the macroscopic concentration $\boldsymbol{C}$ given in the main text, and defining also $P^C(\boldsymbol{c}, t) = n_0 P(n_0 \boldsymbol{c}, t)$ and $M_i^C(t; \boldsymbol{c}) = M_i(t; n_0 \boldsymbol{c})/n_0$, we can write

$$\left(\prod_j \mathbb{E}_j^{-s_{ij}} - 1 \right) P(\boldsymbol{n}, t') M_i(t - t'; \boldsymbol{n}) \approx -\frac{\boldsymbol{s}_i}{n_0} \cdot \nabla P^C(\boldsymbol{c}, t') M_i^C(t - t'; \boldsymbol{c}) . \tag{C1}$$

Also, for large particle numbers, we have for the sum over particle numbers (to be understood component by component) $\sum_{\boldsymbol{n}} \approx n_0 \int d\boldsymbol{c}$. Thus, multiplying Eq. (4) by, and summing over, $\boldsymbol{n}$, using the above approximations, and integrating over $\boldsymbol{c}$ by parts, we arrive at Eq. (6).

Appendix D: Generalized Gillespie algorithm

As discussed in the main text, the intrinsic reaction waiting times should be exponentially distributed, $p_i(t) = \kappa_i \exp(-\kappa_i t)$, which recovers the classical Gillespie algorithm in the absence of global delay. From Eq. (7) in the main text we then obtain

$$\psi_i^r(t; \boldsymbol{n}) = h_i(\boldsymbol{n}) \kappa_i \exp[-\kappa_i h_i(\boldsymbol{n}) t] , \tag{D1}$$

and from Eq. (8) in the main text

$$\phi_i^r(t; \boldsymbol{n}) = h_i(\boldsymbol{n}) \kappa_i \exp\left[-\sum_\ell \kappa_\ell h_\ell(\boldsymbol{n}) t \right] . \tag{D2}$$

The probability ρ_i that reaction i occurs is given by marginalization of the latter over t as

$$\rho_i(\boldsymbol{n}) = \frac{h_i(\boldsymbol{n}) \kappa_i}{\sum_\ell \kappa_\ell h_\ell(\boldsymbol{n})} . \tag{D3}$$

The PDF of reaction waiting times $\phi_{|i}^r$, given that reaction i occurs, is accordingly given by

$$\phi_{|i}^r(t; \boldsymbol{n}) = \sum_\ell \kappa_\ell h_\ell(\boldsymbol{n}) \exp\left[-\sum_k \kappa_k h_k(\boldsymbol{n}) t \right] , \tag{D4}$$

which is independent of i. Based on these two distributions, we can now describe the algorithm, one step of which may be summarized as follows:

  1. Generate a random integer i according to (D3).

2. Generate the reaction waiting time τ^r according to (D4).

3. Generate the global delay time τ^g:

    (a) scenario 1: according to ψ^g.

    (b) scenario 2: generate a random variable η according to a Possion distribution with mean $\gamma\tau^r$, where γ is the (reaction-independent) rate at which delay events occur; generate a series of η random variables $\{\vartheta_k^g\}_{k=1}^{\eta}$ according to ψ_0^g; determine the global delay as $\tau^g = \sum_{k=1}^{\eta}\vartheta_k^g$.

4. Increment time by $\tau^r + \tau^g$.

5. Change the system state according to reaction i.

These procedures are to be repeated until a certain condition is met, such as a certain maximum time being exceeded.

Note that this algorithm may serve two related but slightly different purposes: (i) Directly simulate the dynamics of a reactive system for which the reaction waiting times are known in the context of a CTRW; and (ii) Numerically integrate a known generalized master equation of the form (4) by constructing appropriate reactions.

Appendix E: Scenario 1: Independent global delay

First, let us consider fully independent global delay, distributed according to ψ^g. From Eq. (5), and using Eq. (D2),

$$\tilde{M}_i(\lambda; \boldsymbol{n}) = \frac{\lambda\kappa_i h_i(\boldsymbol{n})\tilde{\psi}^g(\lambda)}{\lambda + [1 - \tilde{\psi}^g(\lambda)]\sum_\ell \kappa_\ell h_\ell(\boldsymbol{n})} \ . \tag{E1}$$

For a finite mean global delay such that $\langle\tau^g\rangle = \mu < \infty$, we approximate $\tilde{\psi}^g(\lambda) \approx 1 - \mu\lambda$ for $\lambda \ll \mu^{-1}$, which gives

$$\tilde{M}_i(\lambda; \boldsymbol{n}) \approx \frac{\kappa_i h_i(\boldsymbol{n})}{1 + \mu\sum_\ell \kappa_\ell h_\ell(\boldsymbol{n})} \ . \tag{E2}$$

Appendix F: Scenario 2: Global delay as a compound Poisson process

1. Memory function

For exponentially distributed intrinsic waiting times we obtain the exact result

$$\tilde{M}_i(\lambda; \boldsymbol{n}) = \frac{h_i(\boldsymbol{n})\kappa_i\lambda}{\lambda + \gamma[1 - \tilde{\psi}_0^g(\lambda)]} \ . \tag{F1}$$

Now assume that the trapping times have infinite mean and some characteristic time scale μ, such that $\tilde{\psi}_0^g(\lambda) \approx 1 - (\mu\lambda)^\beta$ for $\lambda \ll \mu^{-1}$, with $0 < \beta < 1$. For $\lambda \ll t_w^{-1} = (\gamma\mu^\beta)^{1/(1-\beta)}$ we find

$$\tilde{M}_i(\lambda; \boldsymbol{n}) \approx h_i(\boldsymbol{n})\kappa_i(t_w\lambda)^{1-\beta} \ . \tag{F2}$$

2. Moment asymptotics for infinite-mean delay

In order to obtain the asymptotic behavior for concentration moments arising from Eq. (12), we first consider its Laplace transform,

$$\lambda\langle\tilde{\boldsymbol{C}}\rangle = \boldsymbol{C}_0 + \sum_i \boldsymbol{s}_i\kappa_i^C(t_w\lambda)^{1-\beta}\mathcal{L}\{\langle\prod_j C_j^{r_{ij}}\rangle\} \ , \tag{F3}$$

where $\mathcal{L}\{\cdot\}$ denotes the Laplace transform. Now, for an order α annihilation reaction $\sum_{i=1}^{\alpha}\mathcal{S}_i \to \varnothing$ with equal initial concentrations c_0, we have $C_i(t) = C(t)$ for all species i and all times t due to the initial condition and the reaction stoichiometry, and we obtain

$$\lambda\langle\tilde{C}\rangle = c_0 - \kappa^C(t_w\lambda)^{1-\beta}\mathcal{L}\{\langle C^\alpha\rangle\} \ . \tag{F4}$$

For small λ (late times), the dominant terms in this equation are the two on the right hand side. Solving for $\mathcal{L}\{\langle C^\alpha \rangle\}$ and inverting the Laplace transform yields directly

$$\frac{\langle C^\alpha(t) \rangle}{c_0^\alpha} \approx \frac{1}{\Gamma(1-\beta)} \left(\frac{t_r}{t_w} \right)^{1-\beta} \left(\frac{t}{t_r} \right)^{-\beta} , \tag{F5}$$

where $t_r = 1/(\kappa^C c_0^{\alpha-1})$, $t_w = (\gamma \mu^\beta)^{-1/(1-\beta)}$, and Γ is the Gamma function, for $t \gg \mu, t_w, t_r(t_r/t_w)^{(1-\beta)/\beta}$.

3. Subordination approach

The generalized chemical master equation for exponential intrinsic reaction times reads in Laplace space as

$$\lambda \tilde{P}(\boldsymbol{n}, \lambda) = \tilde{P}(\boldsymbol{n}, 0) + \sum_i \left(\prod_j \mathbb{E}_j^{-s_{ij}} - 1 \right) \tilde{P}(\boldsymbol{n}, \lambda) \frac{h_i(\boldsymbol{n}) \kappa_i \lambda}{\lambda + \gamma[1 - \tilde{\psi}_0^g(\lambda)]} . \tag{F6}$$

Specifically, for $\tilde{\psi}_0^g \approx 1 - (\mu \lambda)^\beta$, we obtain

$$\lambda \tilde{P}(\boldsymbol{n}, \lambda) \approx \tilde{P}(\boldsymbol{n}, 0) + \sum_i \left(\prod_j \mathbb{E}_j^{-s_{ij}} - 1 \right) \tilde{P}(\boldsymbol{n}, \lambda) \frac{h_i(\boldsymbol{n}) \kappa_i}{1 + (t_w \lambda)^{\beta-1}} , \tag{F7}$$

where $t_w = (\gamma \mu^\beta)^{1/(\beta-1)}$. Note that for a fixed finite t_w, this equation is exact for all λ in the scaling limit $\mu \to 0$, $\gamma \to \infty$. We can write (F7) as

$$[\lambda + (t_w \lambda)^\beta / t_w] \tilde{P}(\boldsymbol{n}, \lambda) = [1 + (t_w \lambda)^{\beta-1}] \tilde{P}(\boldsymbol{n}, 0)$$
$$+ \sum_{i=1}^{m_r} \left(\prod_j \mathbb{E}_j^{-s_{ij}} - 1 \right) \tilde{P}(\boldsymbol{n}, \lambda) h_i(\boldsymbol{n}) \kappa_i . \tag{F8}$$

It has the same form as the Laplace transform of the chemical master for P_{wm} in the well-mixed scenario,

$$\lambda \tilde{P}_{wm}(\boldsymbol{n}, t) = P_{wm}(\boldsymbol{n}, 0) + \left(\prod_j \mathbb{E}_j^{-s_{ij}} - 1 \right) \tilde{P}_{wm}(\boldsymbol{n}, \lambda) h_i(\boldsymbol{n}) \kappa_i , \tag{F9}$$

where the subscript wm denotes *well mixed*. Thus, $\tilde{P}$ can be expressed in terms of $\tilde{P}_{wm}$ as

$$\tilde{P}(\boldsymbol{n}, \lambda) = [1 + (t_w \lambda)^{\beta-1}] \tilde{P}_{wm}[\boldsymbol{n}, \lambda + (t_w \lambda)^\beta / t_w] . \tag{F10}$$

The latter can also be obtained by subordination with the time process

$$dT(u) = du + t_w (du/t_w)^{1/\beta} \xi(u) , \tag{F11}$$

where the $\xi(u)$ are independent unit (i.e., with unit characteristic time) Lévy β-stable random variables. We then obtain for P

$$P(\boldsymbol{n}, t) = \int_0^\infty du \, P_{wm}(\boldsymbol{n}, u) h(u, t) , \tag{F12}$$

where $h(u, t) = \delta[u - U(t)]$, with $U(t) = \max[u | T(u) \leq t]$. We note now that

$$\int_u^\infty du' \, h(u', t) = \int_0^t dt' \, l(t', u) , \tag{F13}$$

where $l(t, u) = \langle \delta(t - T(u)) \rangle$. We obtain for their Laplace transforms

$$\tilde{h}(u, \lambda) = -\lambda^{-1} \partial_u \tilde{l}(\lambda, u) . \tag{F14}$$

The Laplace transform of $l(t, u)$ is

$$\tilde{l}(\lambda, u) = e^{-[\lambda + (t_w \lambda)^\beta / t_w] u} , \tag{F15}$$

and therefore

$$\tilde{h}(u, \lambda) = [1 + (t_w \lambda)^{\beta-1}] e^{-[\lambda + (t_w \lambda)^\beta / t_w] u} . \tag{F16}$$

Using the latter in the Laplace transform of (F12) gives for $\tilde{P}$

$$\tilde{P}(\boldsymbol{n}, \lambda) = [1 + (t_w \lambda)^{\beta-1}] \int_0^\infty du P_{wm}(\boldsymbol{n}, u) e^{-[\lambda + (t_w \lambda)^\beta / t_w] u} , \tag{F17}$$

which is equivalent to (F10).

Thus, we may calculate the ensemble average of $\tilde{C}$ as

$$\langle \tilde{C}(\lambda) \rangle = [1 + (t_w \lambda)^{\beta-1}] \langle \tilde{C}_{wm}[\lambda + (t_w \lambda)^\beta / t_w] \rangle . \tag{F18}$$

Annihilation Reaction $\alpha = 2$

We now compute $\tilde{C}$ for the reaction $\mathcal{S}_1 + \mathcal{S}_2 \to \varnothing$ with equal initial conditions c_0 for both species. Due to the stoichiometry and the initial condition, we have $C_1(t) = C_2(t) = C(t)$ for all times $t \geqslant 0$. The well-mixed solution is also the same for each species, $\langle C_{wm}(t) \rangle = c_0/(1 + t/t_r)$, with $t_r = 1/(\kappa^C c_0)$. Taking the Laplace transform of the well-mixed solution and using Eq. (F18) leads to

$$\frac{\langle \tilde{C}(\lambda) \rangle}{c_0} = -[1 + (t_w \lambda)^{\beta-1}] t_r e^{t_r \lambda} \text{Ei}[t_r (\lambda + (t_w \lambda)^\beta / t_w)] , \tag{F19}$$

where $\text{Ei}(x) = \int_{-x}^\infty dy \, e^{-y}/y$ is an exponential integral.

To determine the late-time behavior, we consider the following expansion around $x = 0$,

$$\text{Ei}(x) = \gamma_E + \ln(|x|) + \mathcal{O}(x) , \tag{F20}$$

where $\gamma_E = -F(1)$ is the Euler–Mascheroni constant, with F the digamma function. This leads to

$$\frac{\langle \tilde{C}(\lambda) \rangle}{c_0} \approx -\frac{t_r \beta}{(t_w \lambda)^{1-\beta}} \ln \left[\left(\frac{e^{\gamma_E} t_r}{t_w} \right)^{1/\beta} t_w \lambda \right] , \tag{F21}$$

for $\lambda \ll t_r^{-1}, t_w^{-1}, \mu^{-1}, t_r^{-1}(t_r/t_w)^{-(1-\beta)/\beta}$. Using the inverse Laplace transform $\mathcal{L}^{-1}\{\ln \lambda / \lambda\} = -(\gamma_E + \ln t)$, we obtain

$$\frac{\langle C(t) \rangle}{c_0} \approx \frac{t_r}{t_w^{1-\beta}} \beta \partial_t^\beta \ln \left[\left(\frac{t_w}{e^{\gamma_E(1-\beta)} t_r} \right)^{1/\beta} \frac{t}{t_w} \right] . \tag{F22}$$

The fractional derivative of the logarithm can be computed explicitly [51]. For $0 < \beta < 1$,

$$\partial_x^\beta \ln x = \frac{x^{-\beta}}{\Gamma(1-\beta)} [\ln x - \gamma_E - F(1-\beta)] , \tag{F23}$$

and we obtain, in terms of t/t_r,

$$\frac{\langle C(t) \rangle}{c_0} \approx \left(\frac{t_r}{t_w} \right)^{1-\beta} \left(\frac{t}{t_r} \right)^{-\beta} \frac{\beta}{\Gamma(1-\beta)} \left(\ln \left[\left(\frac{t_w}{t_r} \right)^{\frac{1-\beta}{\beta}} \frac{t}{t_r} \right] - \frac{\gamma_E}{\beta} - F(1-\beta) \right) . \tag{F24}$$

Annihilation Reaction $\alpha = 1$

Higher order moments of concentration may also be obtained using the subordination approach for this and other reaction setups. For example, we may easily obtain all integer-order moments for a first order annihilation reaction $\mathcal{S}_1 \to \varnothing$. First, we consider the appropriate well-mixed solution, which in this case is given by $\langle C_{wm}(u) \rangle = c_0 e^{-\kappa^C u} = c_0 e^{-u/t_r}$. The mth order moment is then given by the formula

$$\langle C_1^m(t) \rangle = \int_0^t \mathrm{d}u \, \langle C_{wm}(u) \rangle^m h(u, t) \,, \tag{F25}$$

where we have used the closure $\langle C_{wm}^m(u) \rangle = \langle C_{wm}(u) \rangle^m$, which holds for the well mixed process. Using the same approach as above, we can easily solve this integral by considering the Laplace transform, and we obtain

$$\frac{\mathcal{L}\{\langle C_1^m \rangle\}}{c_0^m} = \frac{t_r + t_r(t_w\lambda)^{\beta-1}}{m + (t_r/t_w)(t_w\lambda)^\beta + t_r\lambda} \,, \tag{F26}$$

which yields, for late times $t \gg t_r, t_w, t_r(t_r/t_w)^{(1-\beta)/\beta}/m$,

$$\frac{\langle C_1^m(t) \rangle}{c_0^m} = \frac{1}{m\Gamma(1-\beta)} \left(\frac{t_r}{t_w} \right)^{1-\beta} \left(\frac{t}{t_r} \right)^{-\beta} \,. \tag{F27}$$

Notice how the first order moment agrees with that obtained from Eq. (12), see Eq. (F5).