Stochastic Processes with Distributed Delays: Chemical Langevin Equation and Linear-Noise Approximation

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(Received 26 February 2013; published 18 June 2013)

We develop a systematic approach to the linear-noise approximation for stochastic reaction systems with distributed delays. Unlike most existing work our formalism does not rely on a master equation; instead it is based upon a dynamical generating functional describing the probability measure over all possible paths of the dynamics. We derive general expressions for the chemical Langevin equation for a broad class of non-Markovian systems with distributed delay. Exemplars of a model of gene regulation with delayed autoinhibition and a model of epidemic spread with delayed recovery provide evidence of the applicability of our results.

DOI: 10.1103/PhysRevLett.110.250601 PACS numbers: 05.40.−a, 02.30.Ks, 02.50.Ey, 05.10.Gg

Introduction.—The theory of discrete Markov processes is well established, and has found applications in a variety of disciplines, including biology, chemistry, physics, evolutionary dynamics, finance, and the social sciences [1]. The standard mathematical treatment is the chemical master equation [2]. Exactly soluble problems are an exception, although they include notable examples such as the voter model [3]. The majority of Markovian systems can only be analyzed using approximative schemes, e.g., the van Kampen or the Kramers-Moyal expansions [2,4,5]. Truncating these expansions after subleading order leads to a Gaussian approximation, the so-called chemical Langevin equation [6]. When linearized about a deterministic trajectory this is known as the linear-noise approximation (LNA) in chemistry and biology [4]. The Gaussian approximation and the LNA provide an important starting point for further analytical studies and for efficient simulations [6,7]. Analytical approaches of this type have been applied to a wide range of problems [8], and for many model systems they reflect the current state of play. Schemes going beyond Gaussian order are only currently being constructed [9]. The purpose of our work is to develop a comprehensive picture of the LNA for interacting-particle systems with delay. The time evolution of delay systems depends on the prior path the system has taken. Existing approaches include Fokker-Planck equations [10] and time-scale separation [11]. The system-size expansion to first order has been carried out in Refs. [11,12] for a model with one fixed delay time. Recent work [13] has extended these approaches to systems with distributed delays. These are recognized as more realistic than models with constant delays [14–16], but a comprehensive formalism is still lacking.

Most existing work on stochastic delay models is based on extensions of the master equation for delay systems. We take a different approach and choose a generating function description of entire paths of the dynamics [17]. This formalism is originally due to Martin, Siggia, Rose, Janssen, and De Dominicis (MSRJD), and it is not to be confused with a generating function approach to solving master equations. The MSRJD formalism removes the need for a master equation altogether. This provides a new perspective on stochastic delay systems, and, we think, it allows one to carry out the LNA more naturally and systematically. As a consequence we are able to derive an explicit Gaussian approximation for a broad class of delay models, ready to be applied to problems with delay dynamics in a number of fields.

Generating functional approach to delay systems.—Consider a reaction system with S types of particles, $\alpha = 1, \ldots, S$. The state of the system is characterized by $\mathbf{n}(t) = (n_1(t), \ldots, n_S(t))$, where the integer $n_\alpha(t)$ indicates the number of particles of type α at time t. The dynamics occurs via R possible reactions, $i = 1, \ldots, R$. The rate with which reaction i fires is denoted by $T_i(\mathbf{n})$. Each reaction can result in a change of particle numbers at the time the reaction is triggered, and at a later time. The latter aspect reflects the delay interaction. We write $\nu_{i,\alpha}$ for the change in the number of particles of type α at the time a reaction of type i is triggered. Additionally when a reaction of type i fires at time t a delay time $\tau > 0$ is drawn from a distribution $K_i(\cdot)$. A further change of particle numbers occurs at time $t + \tau$, indicated by the variables $w^\tau_{i,\alpha}$. This description includes Markovian processes; one then has $w^\tau_{i,\alpha} = 0$.

The purpose of expansion methods is to construct Gaussian stochastic differential equations (SDEs) approximating the statistics of the reaction dynamics [2,4]. These procedures rely on a large parameter N, in most cases a scale setting the number of particles in the system. Time is scaled so that reaction rates are of order N, $T_i(\mathbf{n}) = Nr_i(\mathbf{x})$, and relative particle numbers $x_\alpha = n_\alpha/N$ are introduced. An expansion in negative powers of N then leads to an effective SDE for $\mathbf{x}$, valid in the limit of large, but finite N. Equivalent effective SDEs can be obtained using a theorem due to Kurtz [18]. These techniques, however, are only applicable for Markovian systems.

The starting point for our generating function approach is a discretized dynamics. Introducing a time step Δ we assume that the number of reactions of type i firing at time step t and with a delayed effect precisely $\tau \in \mathbb{N}\Delta$ time steps later is a Poissonian random variable $k_{i,t}^{\tau}$ with mean $Nr_i[\mathbf{x}(t)]K_i(\tau)\Delta^2$ [19,20]. We will write $\mathcal{P}(\mathbf{k})$ for their joint distribution, suppressing the dependence on $\mathbf{x}$. The generating function for the discrete-time process is then given by

$$Z[\boldsymbol{\psi}] = \sum_{\mathbf{k}} \int D\mathbf{x}\mathcal{P}(\mathbf{k}) \exp\left(i\Delta \sum_{t,\alpha} \psi_{\alpha,t} x_{\alpha,t}\right) \times \prod_{t,\alpha} \delta[x_{\alpha,t+\Delta} - x_{\alpha,t} - \phi_\alpha(\mathbf{k})]. \quad (1)$$

We have here introduced the source term $\boldsymbol{\psi}$ whose role is to generate the moments of the $\{x_{\alpha,t}\}$. The (rescaled) total change of the number of particles of type α at time step t is given by

$$\phi_\alpha(\mathbf{k}) = N^{-1} \sum_i \left(k_{i,t} v_{i,\alpha} + \sum_{\tau \geq \Delta} k_{i,t-\tau}^{\tau} w_{i,\alpha}^{\tau}\right), \quad (2)$$

where $k_{i,t} = \sum_{\tau \geq \Delta} k_{i,t}^{\tau}$. By writing the δ functions in Eq. (1) in their exponential representation, performing the average over the $\{k_{i,t}^{\tau}\}$, keeping only leading and subleading terms in an expansion in powers of N^{-1}, and subsequently taking the limit $\Delta \to 0$ a continuous-time generating functional is obtained. These steps are described in detail in the Supplemental Material [19]. The resulting generating functional is equivalent to the Gaussian dynamics

$$\dot{x}_\alpha = F_\alpha(t, \mathbf{x}) + N^{-1/2}\eta_\alpha, \quad (3)$$

with $\langle \eta_\alpha(t)\eta_\beta(t')\rangle = B_{\alpha,\beta}(t, t', \mathbf{x})$, and where

$$F_\alpha(t, \mathbf{x}) = \sum_i \left[r_i[\mathbf{x}(t)]v_{i,\alpha} + \int_0^\infty d\tau K_i(\tau) r_i[\mathbf{x}(t-\tau)] w_{i,\alpha}^{\tau} \right]. \quad (4)$$

We set $K_i(\tau) = 0$ for $\tau < 0$, and introduce

$$B_{\alpha,\beta}(t, t', \mathbf{x}) = \sum_i \Big\{ \delta(t-t') \Big[r_i[\mathbf{x}(t)] v_{i,\alpha} v_{i,\beta} + \int_0^\infty d\tau r_i[\mathbf{x}(t-\tau)] K_i(\tau) w_{i,\alpha}^{\tau} w_{i,\beta}^{\tau} \Big] + [r_i[\mathbf{x}(t)] K_i(t'-t) v_{i,\alpha} w_{i,\beta}^{(t'-t)} + r_i[\mathbf{x}(t')] K_i(t-t') v_{i,\beta} w_{i,\alpha}^{(t-t')}] \Big\}. \quad (5)$$

Equations (3)–(5), define the chemical Langevin equation for systems with distributed delay. They are the main result of our Letter and provide general expressions for the Gaussian approximation of a wide class of delay systems [21,22]. These equations allow one to disentangle the contributions of the different reactions to the noise, and they can be used for efficient numerical simulations. The gain in computing time can be significant (see the Supplemental Material [19] for further details). The result of Eqs. (3)–(5) is slightly stronger than the LNA [2], which can be obtained from a straightforward linearization (see the Supplemental Material [19]). The resulting linear dynamics is an important intermediate step for further analytical investigations. In the following we will demonstrate the applicability of this approach. We will use our results to compute the spectra of noise-induced quasicycles [23] in a model of gene regulation and in a model of epidemic spread, both with delay interactions.

Application to a model of gene regulation.—Delays in transcription and translation play an important role in gene regulation. They are considered a potential mechanism for oscillatory behavior in somitogenesis, giving rise to spatially heterogeneous cellular structures [24,25]. Models of these processes have traditionally focused on differential equations (see, e.g., Ref. [25]). It is only more recently that intrinsic noise has been included [11,26]. This is due to the observation that particle numbers in gene regulatory systems can be small, making deterministic approximations inadequate [27]. For example noise-driven quasicycles go undetected in deterministic models [23]. Existing theoretical analyses are limited to models with constant delay periods [11,12]; we note recent advances [13]. Our result for systems with distributed delay provides a systematic theoretical framework, and we apply it to the simple model of gene regulation described in Refs. [25,26]. We consider two types of particles: mRNA molecules, denoted by M, and protein molecules P. The stochastic dynamics are given by

$$M \xrightarrow{\mu_M} \varnothing, \qquad P \xrightarrow{\mu_P} \varnothing, \qquad M \xrightarrow{\alpha_P} M + P, \qquad \varnothing \overset{g(n_P),K(\tau)}{\Longrightarrow} M. \quad (6)$$

The first two interactions correspond to degradation of mRNA and protein, respectively; the constant model parameters μ_M and μ_P describe their degradation rates. The third interaction describes the translation of mRNA into protein. Finally, the fourth interaction represents the transcription process, within the model effectively the production of mRNA. This process is suppressed by the presence of protein molecules, as reflected by the Hill function $g(n_P) = \alpha_M[1 + [n_P/(P_0 N)]^h]^{-1}$, where h and P_0 are constants. The double arrow indicates a delay reaction. In this particular model the reaction has no effect on particle numbers at the time t it is triggered, but only at a later time $t + \tau$, where τ is a distributed delay time drawn from $K(\tau)$. The reaction rate depends on the number of proteins at the earlier time $n_P(t)$. Earlier works [12,26] focus on the case in which $K(\cdot)$ is a δ distribution, and exclude distributed delays. Applying our general result above (see the Supplemental Material [19] for details) we find

$$\dot{x}_M(t) = \alpha_M \int_0^\infty d\tau K(\tau) f[x_P(t-\tau)] - \mu_M x_M(t) + N^{-1/2}\eta_M(t),$$
$$\dot{x}_P(t) = \alpha_P x_M(t) - \mu_P x_P(t) + N^{-1/2}\eta_P(t), \quad (7)$$

where $f[x_P(t)] = [1 + (x_P(t)/P_0)^h]^{-1}$, and

$$\langle \eta_M(t)\eta_M(t')\rangle = \left[\alpha_M \int_0^\infty d\tau K(\tau) f[x_P(t-\tau)] + \mu_M x_M(t)\right]\delta(t-t'),$$
$$\langle \eta_P(t)\eta_P(t')\rangle = [\alpha_P x_M(t) + \mu_P x_P(t)]\delta(t-t'),$$
$$\langle \eta_M(t)\eta_P(t')\rangle = 0. \quad (8)$$

The Gaussian noise components η_M, η_P have no correlations in time, as expected for a dynamics in which each reaction changes particle numbers only at one single time. A more complex case will be studied below. In the deterministic limit $N \to \infty$, Eqs. (7), are found to have a fixed point (x_M^*, x_P^*) for suitable choices of parameters. A systematic expansion $x_M = x_M^* + N^{-1/2}\xi_M$, and similar for x_P, then leads to the LNA: a pair of linear SDEs for the fluctuation variables ξ_M and ξ_P. A straightforward calculation following the lines of Ref. [23] then allows one to compute the power spectra of noise-induced cycles $P_M(\omega) = \langle|\tilde{\xi}_M(\omega)|^2\rangle$, and similarly for the protein (see the Supplemental Material [19]). Results for a uniform distribution of delay times are shown in Fig. 1 and are confirmed convincingly in numerical simulations. In the LNA the stationary distribution for ξ_M and ξ_P can be derived as well (see the Supplemental Material [19] for further results and comparison against simulations).

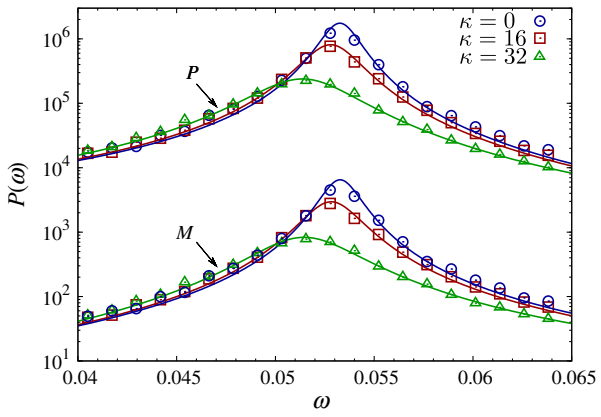

FIG. 1 (color online). Power spectra of quasicycles in the gene regulatory model [15,25,26] with uniformly distributed delays over the interval $[18.7 - \kappa/2, 18.7 + \kappa/2]$ minutes. Lines are theoretical predictions within the LNA; markers are from simulations using a modified next-reaction method [29] and represent data averaged over 700 realizations. Parameters are $\alpha_M = \alpha_P = 1$, $\mu_P = \mu_M = 0.03$ (all with units min^{-1}), $P_0 = 10$, $h = 4.1$, $N = 5000$.

Application to a model of epidemic spread with delayed recovery.—We consider a variant of the susceptible-infective-recovered (SIR) model with birth and death [16]. The model describes a population of N individuals, each of which can be in one of three states, S, I, or R. Infection occurs via the process $S + I \xrightarrow{\beta} 2I$, and the newly infected individual may recover ($I \to R$) at a later time, where the delay is drawn from a distribution $H(\cdot)$. All individuals are subject to a birth-death process, occurring with rate μ, and in which an individual dies and is immediately replaced by an individual of type S. This is a commonly used simplification, ensuring a constant population size [16]. This setup implies that a newly infected individual may die and be replaced by an individual of type S before its designated recovery time is reached. This is illustrated in Fig. 2. Assume an infection occurs at time t. One may think of the subsequent dynamics as follows: at the time of infection, a designated time to recovery τ is drawn from $H(\cdot)$. At the same time a designated time to removal s is drawn from an exponential distribution $E(s) = \mu e^{-\mu s}$. There are then two possible subsequent courses of events. In case (i), if $\tau < s$, recovery occurs before death, the recovery process completes at time $t + \tau$, and the infective individual is replaced by an individual of type R. The death event is discarded. The probability for case (i) to occur is $\chi = \int_0^\infty d\tau H(\tau) \int_\tau^\infty ds E(s)$. Conditioned on this sequence of events, i.e., if recovery occurring before death is a given, the time to recovery follows the distribution $K(\tau) = \chi^{-1} H(\tau) \int_\tau^\infty ds E(s)$. Case (ii) describes the opposite situation $s < \tau$ occurring with probability $1 - \chi$. In this case the newly infected individual dies before the designated time of recovery, and we have a reaction of type $I \to S$ at time $t + s$. The conditional time to removal, given that case (ii) is realized,

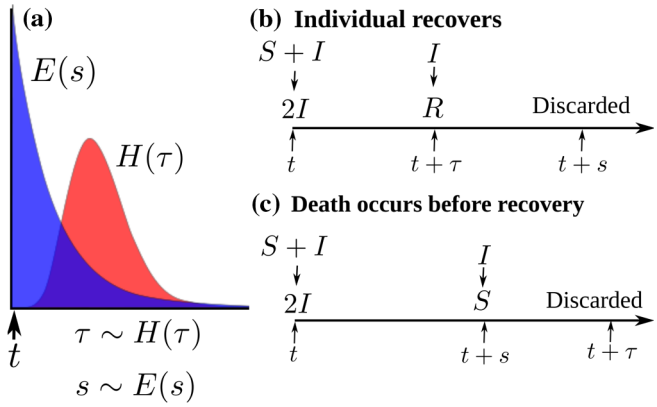

FIG. 2 (color online). Possible sequences of events when a reaction with delayed recovery is triggered. A time to death s, and a time to recovery τ are drawn from the appropriate distributions [panel (a)]. Depending on the outcome recovery or death may occur [panels (b) and (c), respectively], the remaining event is discarded.

is $Q(s) = (1-\chi)^{-1}E(s)\int_s^\infty d\tau H(\tau)$. We can summarize the reaction scheme as follows:

$$R \xrightarrow{\mu} S,$$
$$S + I \xrightarrow{\chi\beta} 2I; \qquad I \xrightarrow{K(\tau)} R, \tag{9}$$
$$S + I \xrightarrow{(1-\chi)\beta} 2I; \qquad I \xrightarrow{Q(s)} S.$$

The notation for the second reaction channel, occurring with rate $T_2(\mathbf{n}) = \beta\chi n_S n_I/N$, indicates that one particle of type S is converted into an I at the time the reaction is triggered, and that an individual of type I is converted to R at a later time $t+\tau$, where τ is drawn from the distribution $K(\cdot)$. Similarly, the third reaction channel fires with rate $T_3(\mathbf{n}) = \beta(1-\chi)n_S n_I/N$, and results in an event $S + I \to 2I$ at the time the reaction is triggered, and then in an event of type $I \to S$ at a later time $t+s$, where s is drawn from the distribution $Q(\cdot)$.

Applying the general result above we find (with $S = n_S/N$, $I = n_I/N$),

$$\dot{S}(t) = -\beta S(t)I(t) + \mu(1 - S(t) - I(t)) + \beta(1-\chi) \times \int_{-\infty}^{t} dt' Q(t-t')S(t')I(t') + N^{-1/2}\eta_S(t),$$
$$\dot{I}(t) = \beta S(t)I(t) - \beta\int_{-\infty}^{t} dt' S(t')I(t')[\chi K(t-t') + (1-\chi)Q(t-t')] + N^{-1/2}\eta_I(t). \tag{10}$$

Unlike in the above model of gene regulation, the noise is now correlated in time. Expressions for the correlation matrix are lengthy and are reported in the Supplemental Material [19].

Recent theoretical work has studied SIR models in which individuals progress through a series of L infectious 'stages' $I_1 \to I_2 \to \cdots \to I_L \to R$ at rate γL before they recover (or die along the way) [16]. In our formalism this is equivalent to a model in which $H(\cdot)$ is a Γ distribution $H(\tau) = ((\gamma L)^L/\Gamma(L))\tau^{L-1}e^{-\gamma L\tau}$. To make contact with the results of Ref. [16] we use Eqs. (10) to compute the power spectra of noise-driven quasicycles about the fixed point of the deterministic limiting dynamics (see the Supplemental Material [19]). Results from the theory and from simulations are shown in Fig. 3. We find that simulations of the staged model are less costly than those of the delay model. However the analytical calculation of the results in Fig. 3 is more demanding in the staged model, as it involves a larger number of particle types. For sufficiently small values of the death rate μ there is no noticeable difference between the predictions of our approach and the result of Ref. [16] (see the main panel of Fig. 3). This latter result is based on an expansion in μ and deviates from simulations when the small-μ approximation is not justified. Our theory does not rely on such approximations, and describes simulation results accurately in such cases (see the inset of Fig. 3). The staged model is limited to Γ-distributed recovery times, whereas our approach is more general and applies to other delay kernels suggested in the literature [28]. Additional results can be found in the Supplemental Material [19].

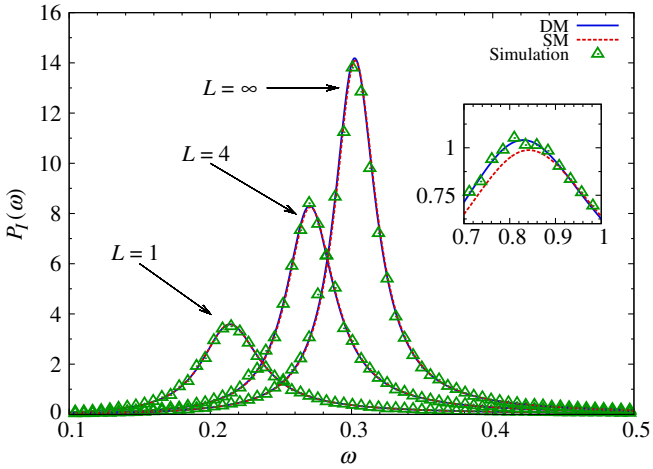

FIG. 3 (color online). Power spectra $P_I(\omega)$ for the SIR model with delayed recovery. Lines show results from the LNA for the staged model (SM) (see Refs. [16,30]), and for the delay model (DM). Markers are from simulations (SM for $L = 1$ and $L = 4$, DM for $L = \infty$), averaged over 800 independent runs. Model parameters are $\beta = 10.56$, $\mu = 4.81 \times 10^{-3}$, $\gamma = 1$. System size is $N = 10^6$. Inset: Results for $L = 4$ and $\mu = 4.81 \times 10^{-2}$.

Conclusions.—We have presented a comprehensive approach to the LNA for stochastic dynamics with distributed delays. Our calculation is based on a generating functional, rather than a master equation. We focus on probabilities to observe entire paths of the dynamics. This makes the approach suitable for non-Markovian systems, and we are able to derive general expressions for the Gaussian approximation of a broad class of processes with distributed delays. The resulting nonlinear chemical Langevin equation cannot normally be solved analytically, but it can be used for efficient simulations. Further analytical progress can be made in the linear-noise approximation. The validity of our results is demonstrated through the computation of power spectra of noise-driven cycles in delay models of gene regulation and of epidemic spread. We expect that the general expressions we have derived will be of use for studies of a variety of phenomena in the biological and physical sciences, and indeed in other areas where individual-based models with delayed interactions are relevant.

T. B. acknowledges support from the EPSRC. T. G. is supported by RCUK (reference EP/E500048/1).

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[19] See Supplemental Material at http://link.aps.org/supplemental/10.1103/PhysRevLett.110.250601 for further details of the path-integral calculation, and for additional numerical and analytical results.

[20] For $\Delta > 0$ the model dynamics can lead to unphysical negative particle numbers with finite probability. In the limit $\Delta \to 0$, taken at the end of the calculation, this probability vanishes.

[21] We assume that any reaction induces changes in particle numbers at (at most) one later time. Extensions to cases in which changes occur at multiple later times are relatively straightforward.

[22] In the Markovian case ($w^{\tau}_{i,\alpha} = 0$) our result reduces to that obtained from a Kramers-Moyal expansion or from Kurtz' theorem. The Gaussian noise $\boldsymbol{\eta}(t)$ is then white, and the retarded interaction term in F_α is absent.

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[30] The scaling of time (and hence frequencies ω) in Ref. [16] is different from the conventions we use here.