Stochastic Liouville equation for particles driven by dichotomous environmental noise

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We analyze the stochastic dynamics of a large population of non-interacting particles driven by a global environmental input in the form of a dichotomous Markov noise process (DMNP). The population density of particle states evolves according to a stochastic Liouville equation with respect to different realizations of the DMNP. We then exploit the connection with previous work on diffusion in randomly switching environments, in order to derive moment equations for the distribution of solutions to the stochastic Liouville equation. We illustrate the theory by considering two simple examples of dichotomous flows, a velocity jump process and a two-state gene regulatory network. In both cases we show how the global environmental input induces statistical correlations between different realizations of the population density.

I. INTRODUCTION

Recently we analyzed a stochastic Fokker-Planck equation (FPE) describing the evolution of a large population of non-interacting Brownian particles subject to a common environmental input in the form of an Ornstein-Uhlenbeck process [1]. For a given realization of the OU process, the density of particle positions $P(x,t)$ satisfies a deterministic, non-autonomous FPE parameterized by the OU process. However, since the OU process is itself stochastic, this means that different realizations of the OU process generate a distribution of probability densities. We derived moment equations for the distribution of solutions to the stochastic FPE and highlighted the fact that although the particles are non-interacting, the presence of a common environmental input induces statistical correlations. In particular

$$\mathbb{E}[P(x,t)P(y,t)] \neq \mathbb{E}[P(x,t)]\mathbb{E}[P(y,t)],$$

where expectation is taken with respect to different realizations of the environmental noise. We illustrated this result using perturbation theory to calculate the above two-point correlation function close to the white-noise limit of the environmental OU process. We also gave another example of environmentally-induced correlations by reformulating the theory of noise-induced synchronization [2–4] within the stochastic FPE framework.

In this paper we further explore the issue of statistical correlations induced in a population of non-interacting particles driven by a common environmental noise source. Here, however, each particle undergoes piecewise deterministic dynamics rather than Brownian motion, and is driven by a global environmental input consisting of a dichotomous Markov noise process (DMNP) rather than an OU process. The resulting population density evolves according to a stochastic Liouville equation rather than a stochastic FPE. Dichotomous noise has played an important role in the study of non-equilibrium systems over the years, as summarized in the review by Bena [5]. In particular, it provides a more analytically tractable model of colored noise and the effects of finite correlation times than the OU process. Moreover, there are a wide range of physical and biological systems where a DMNP is a good

representation of non-equilibrium processes. For example, within the context of cell biology there are a number of simple examples where some continuous variable $x(t)$ randomly jumps between two forms of deterministic dynamics, depending on the state of some discrete variable $n(t) \in \{0,1\}$ that evolves according to a two-state Markov process [6]: (i) A gene regulatory network where $n(t)$ specifies whether the gene is active or inactive, and $x(t)$ represents the concentration of protein synthesized by the gene. (ii) A stochastic ion channel for which $n(t)$ specifies whether the channel is open or closed and $x(t)$ is membrane voltage. (iii) $x(t)$ represents the position of a molecular motor on a filament track and $n(t)$ specifies whether it is moving to the right with speed v_+ or moving to the left with speed v_- (velocity jump process).

We begin by briefly reviewing the standard theory of a single particle driven by a DMNP in section II. We highlight that the joint probability density of particle and environmental states is given by a Chapman-Kolmogorov equation. In section III, we introduce our population perspective by considering a large population of non-interacting particles driven by the same global DMNP. The resulting density of particle states satisfies a stochastic Liouville equation, from which we construct moment equations for the distribution of probability densities. In sections IV and V we illustrate the theory using simple examples of dichotomous flows, namely, a velocity jump process (section IV) and a two-state gene regulatory network (section V).

II. SINGLE PARTICLE DRIVEN BY DICHOTOMOUS MARKOV NOISE.

Consider a single particle with continuous variable $x(t) \in \Sigma \subset \mathbb{R}$ whose "velocity" switches between two forms

$$v_\pm(x) = f(x) \pm g(x)\Gamma_\pm \qquad (2.1)$$

according to a two-state Markov process with x-independent transition rates $k_\pm$. That is, $x(t)$ evolves according to the following stochastic differential equation

(SDE):

$$\frac{dx}{dt} = f(x) + g(x)\xi(t), \qquad (2.2)$$

where $\xi(t)$ is a realization of the two-state Markov process. In the physics literature $\xi(t)$ is called a dichotomous Markov noise process (DMNP) and is said to act additively if $g(x)$ is independent of x and to act multiplicatively otherwise, see the review by Bena [5] and references therein. It is convenient to rewrite the SDE (2.2) in the form

$$\frac{dx}{dt} = F(x, n(t)), \quad n(t) = 0, 1 \qquad (2.3)$$

with functions

$$F(x, 1) = f(x) + g(x)\Gamma_+, \quad F(x, 0) = f(x) - g(x)\Gamma_-. \qquad (2.4)$$

Comparing Eqs. (2.2) and (2.3) shows that

$$\xi(t) = (\Gamma_+ + \Gamma_-)n(t) - \Gamma_-, \quad n(t) \in \{0, 1\}.$$

The discrete state $n(t)$ evolves according to a two-state Markov chain with matrix generator

$$\mathbf{A} = \begin{pmatrix} -k_+ & k_- \\ k_+ & -k_- \end{pmatrix}. \qquad (2.5)$$

If $P_{nn_0}(t) = \mathbb{P}[N(t) = n | N(0) = n_0]$ then the master equation for the DMNP takes the form

$$\frac{dP_{nn_0}}{dt} = \sum_{m=0,1} A_{nm} P_{mn_0}$$

Using the fact that $P_{0n_0}(t) + P_{1n_0}(t) = 1$ we can solve this pair of equations to give

$$P_{0n_0}(t) = \delta_{0,n_0} e^{-t/\tau_c} + \frac{k_-}{\tau_c}(1 - e^{-t/\tau_c}), \quad \tau_c = \frac{1}{k_- + k_+}.$$

A number of results follow from this. First τ_c is the relaxation time of the DMNP with $P_{mn_0}(t) \to \rho_m$ in the limit $t \to \infty$ and

$$\rho_0 = \frac{k_-}{k_+ + k_-}, \quad \rho_1 = \frac{k_+}{k_+ + k_-}. \qquad (2.6)$$

In the stationary state,

$$\langle \xi(t) \rangle = (\Gamma_+ + \Gamma_-)\langle n(t) \rangle - \Gamma_- = \rho_1 \Gamma_+ - \rho_0 \Gamma_-. \quad (2.7)$$

Suppose, in particular, that the DMNP is unbiased so that $\langle \xi(t) \rangle = 0$. The stationary autocorrelation function is then given by

$$\begin{aligned} \langle \xi(t)\xi(t') \rangle &= \Gamma_-^2 - 2\Gamma_-(\Gamma_+ + \Gamma_-)\rho_1 \\ &\quad + (\Gamma_+ + \Gamma_-)^2 \langle n(t)n(t') \rangle \\ &= \frac{D}{\tau_c} e^{-|t-t'|/\tau_c}, \end{aligned} \qquad (2.8)$$

with noise amplitude $D = k_+ k_- \tau_c^3 (\Gamma_+ + \Gamma_-)^2$. This shows that the DMNP provides an alternative form of colored noise to an Ornstein-Uhlenbeck process.

Given the initial conditions $x(0) = x_0, n(0) = n_0$, introduce the probability density $p_n(x, t|x_0, n_0, 0)$ with

$$\begin{aligned} \mathbb{P}\{x(t) \in (x, x + dx), \, n(t) = n | x_0, n_0\} \\ = p_n(x, t|x_0, n_0, 0)dx. \end{aligned} \qquad (2.9)$$

It follows that $p_n, n = 0, 1$ evolves according to the forward differential Chapman-Kolmogorov (CK) equation [6, 7]

$$\frac{\partial p_0}{\partial t} = -\frac{\partial}{\partial x}(F(x, 0)p_0(x, t)) + k_- p_1 - k_+ p_0, \qquad (2.10a)$$

$$\frac{\partial p_1}{\partial t} = -\frac{\partial}{\partial x}(F(x, 1)p_1(x, t)) + k_+ p_0 - k_- p_1. \qquad (2.10b)$$

(after dropping the explicit dependence on initial conditions). One major topic of interest regarding DMNPs is determining conditions on the functions $F(x, 0)$ and $F(x, 1)$ or, equivalently, $f(x)$ and $g(x)$ for which a stationary solution of Eqs. (2.10a) and (2.10b) exists [5]. This will be illustrated in sections IV and V. In applications one is typically interested in the marginal density $p(x, t) = p_0(x, t) + p_1(x, t)$, which can be used to calculate moments of p such as the mean and variance,

$$\langle x(t) \rangle = \int x p(x, t)dx, \ \text{Var}[x(t)] = \int x^2 p(x, t)dx - \langle x(t) \rangle^2.$$

Then either the moments or the full density profile can be compared with experimentally observed quantities or direct numerical simulations of the SDE (2.3). It is important to note that in making these comparisons one is simultaneously averaging over realizations of the piecewise dynamics and the DMNP. In the next section we will consider a different protocol where one separates out the piecewise dynamics from different realizations of the DMNP.

For simplicity, in this paper we assume that the transition rates $k_\pm$ are independent of the state x. However, in some systems this does not hold, such as gene regulatory networks with feedback, see Sect. V. The solution of Eq. (2.10) now becomes more involved, and one typically has to use some numerical scheme [8].

III. STOCHASTIC LIOUVILLE EQUATION FOR A DICHOTOMOUS FLOW

For a given realization $\sigma(t) = \{n(\tau), 0 \le \tau < t\}$ of the stochastic process $n(t)$, the SDE (2.3) reduces to a deterministic, non-autonomous ODE. Now consider an ensemble of identical, non-interacting particles labeled by $\ell = 1, \ldots, \mathcal{M}$ with state variables $x_\ell(t)$, all being driven
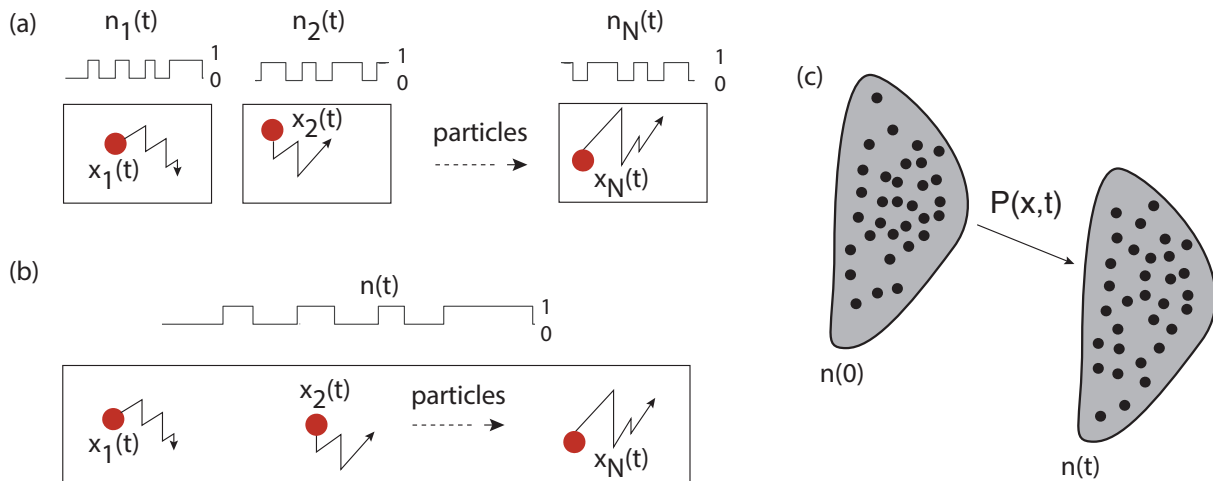
FIG. 1. [Color online] Diagram illustrating the difference between the particle and population or SPDE perspectives. (a) Multiple realizations $(x_j(t), n_j(t))$ of a single particle driven by dichotomous noise generates the density $p_n(x, t)$. (b) Large population $(N \to \infty)$ of particles evolving in a single realization σ of a common dichotomous noise source $n(t)$ generates the density $P(x, t)$. (c) The stochastic Liouville equation describes the evolution of the population density $P(x, t)$ with respect to realizations σ of the common dichotomous noise $n(t)$. A corresponding figure in Ref. [1] shows each particle undergoing Brownian motion rather than piecewise deterministic dynamics, and driven by an OU process rather than a DMNP.

by the same external or environmental variable $n(t)$. Eq. (2.3) becomes

$$\frac{dx_\ell}{dt} = F(x_\ell, n(t)) \qquad (3.1)$$

for $\ell = 1, \ldots, \mathcal{M}$, with the stochastic variable $n(t)$ independent of ℓ and evolving according to a continuous Markov chain with generator $\mathbf{A}$. Assume that the initial positions of the particles, $x_i(0)$, are randomly generated from a density $p_0(x)$. Take the thermodynamic limit $\mathcal{M} \to \infty$, and let $P(x, t)$ denote the density of particles in state x at time t given a particular realization $\sigma(t)$ of the DMNP. The population density evolves according to the stochastic Liouville equation

$$\frac{\partial}{\partial t} P_\sigma(x, t) = \left[-\frac{\partial}{\partial x} F(x, n(t)) \right] P_\sigma(x, t), \qquad (3.2)$$

with $P_\sigma(x, 0) = p_0(x)$. Note that the density $P_\sigma(x, t)$ is a random field with respect to realizations σ.

It is important to highlight the relationship between the stochastic Liouville equation (3.2) and the deterministic CK equation (2.10). In particular, does the former formulation provide any new information that is physically measurable compared to the standard formulation in terms of the CK equation (2.10)? The essential point is that we are dealing with a doubly stochastic process. One source of stochasticity is that the initial condition of each particle is independently generated from some probability density, and the second source of noise is an external input in the form of dichotomous noise. There are then two distinct cases: if the dichotomous noise is independent for each particle (uncorrelated), see Fig. 1(a), then the resulting distribution of sample paths is given by the

solution $p(x, t) = p_0(x, t) + p_1(x, t)$ of the CK equation (2.10). We will refer to this as the *particle perspective*. On the other hand, if the dichotomous noise is common to all the particles (fully correlated), see Fig. 1(b), then the resulting distribution of paths for a single realization σ of the dichotomous noise process is given by the solution $P_\sigma(x, t)$ to the Liouville equation (3.2). We will call this the *SPDE perspective*. (In our previous paper [1], each particle evolved according to an SDE with two sources of noise. The first was intrinsic white noise that was uncorrelated between particles and an environmental or extrinsic colored noise source that was common to all the particles.) From a computational perspective, one can obtain approximations of both densities $p(x, t)$ and $P_\sigma(x, t)$ by partitioning the domain Σ into small bins and counting the number of particles in each bin. The resulting histogram should converge to the appropriate population density in the thermodynamic limit $\mathcal{M} \to \infty$. Clearly both types of population sampling are possible and are thus physically realizable.

The crucial observation is that in the fully correlated case the resulting density $P_\sigma(x, t)$ depends on the particular realization σ. Hence, one could run multiple trails for different σ resulting in a distribution of densities $P_\sigma(x, t)$, as illustrated schematically in Fig. 2 for some fixed time $t = T$. Clearly the set of densities $P_\sigma(x, t)$ for different σ contains more information than the single density $p(x, t)$. For a large number of realizations or trials $\sigma_1, \ldots \sigma_\chi$ and fixed x, t, the computational relationship between the two is $p(x, t) \approx \chi^{-1} \sum_{j=1}^{\chi} P_{\sigma_j}(x, t)$. As we will establish below, a more precise mathematical relationship between the particle and SPDE perspectives can be obtained by deriving moment equations for the distribution ϱ of the resulting stochastic population den-

sity $P_\sigma(x,t)$. In particular, we will find that

$$p(x,t) = \mathbb{E}_\sigma[P_\sigma(x,t)], \qquad (3.3)$$

where the subscript σ denotes expectation with respect to realizations of the DMNP. However, since all particles in the SPDE formulation are driven by a single realization of the same DMNP, it follows that there are higher-order statistical correlations of the density $P_\sigma(x,t)$ even when the particles are otherwise non-interacting so, for example,

$$C(x,y,t) \equiv \mathbb{E}_\sigma[P_\sigma(x,t)P_\sigma(y,t)]$$
$$\neq \mathbb{E}_\sigma[P_\sigma(x,t)]\mathbb{E}_\sigma[P_\sigma(y,t)]. \qquad (3.4)$$

In certain simple cases, however, second-order correlations may disappear in the large t limit (see the example in section IV). (It is important to emphasize that these correlations are at the level of the full probability density function $P_\sigma(x,t)$, which is distinct from correlations in the position of a particle evolving according to some SDE, say, where $\mathbb{E}[x(t)x(t')] \neq \mathbb{E}[x(t)]\mathbb{E}[x(t')]$.) From a computational perspective, we also have the approximation

$$C(x,y,t) \approx \chi^{-1} \sum_{j=1}^{\chi} P_{\sigma_j}(x,t)P_{\sigma_j}(y,t),$$

and similarly for higher-order moments. That is, these moments can be experimentally measured by running multiple realizations of the environment.

Finally, note that the full statistics in the case of fully correlated dichotomous noise is captured by the distribution ϱ of densities P_σ. However, this is a probability functional over an infinite-dimensional space. Therefore, it is more practical to deal with moments of ϱ. It turns out that these moments also have an interpretation in terms of the particle perspective, namely, the nth order moments of ϱ determine the statistics of a population of particle clusters of size n, where each cluster is subject to independent dichotomous noise, but the n particles within a cluster are subject to the same dichotomous noise. This corresponds to having n particles in each box of Fig. 1(a).

A. Moment equations

An analogous distinction between the particle and SPDE perspectives has recently arisen within the context of the diffusion of particles in a randomly switching environment, specifically, a finite domain with randomly switching boundary conditions [9, 10]. Applications in biological physics include diffusion-limited reactions [11], neurotransmission [12], insect physiology [13], and stochastically gated gap junctions [14]. A related work has considered a model of lateral membrane diffusion based on random walks in random environments
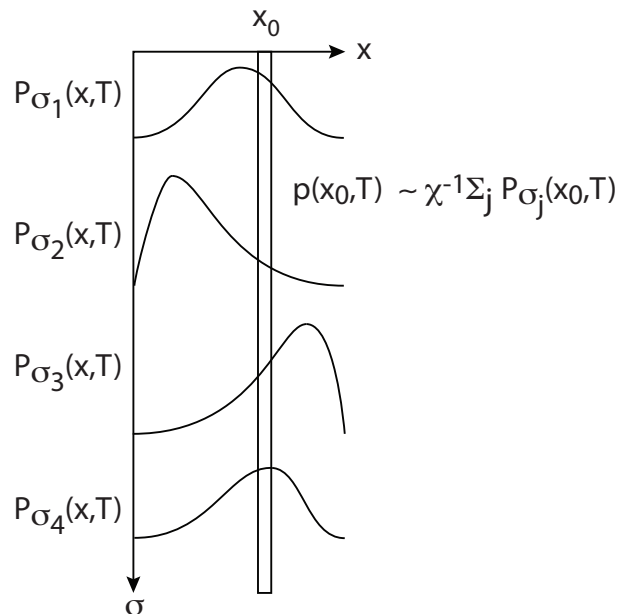

FIG. 2. Schematic illustration of relationship between $p(x,t)$ and $P_\sigma(x,t)$ for a given time $t = T$ and different realizations of the common dichotomous noise, $\sigma = \sigma_j$, $j = 1, \ldots, \chi$.

[15]. As in our previous study of the stochastic FPE arising from a population of Brownian particles driven by a common OU process [1], we will use the moment generating method developed in Ref. [10] to analyze equation (3.2). For ease of notation we drop the index σ from P_σ.

For the sake of illustration, consider the bounded domain $\Sigma = [0, L]$, where we allow the boundary conditions at $x = 0, L$ to be n-dependent. The first step is to discretize Eq. (3.2) using a finite-difference scheme so that the system is converted to a higher-dimensional DMNP. Introduce the lattice spacing a such that $\mathcal{N}a = L$ for integer $\mathcal{N}$, and let $P_j(t) = P(aj,t)$ etc., $j = 0, \ldots, \mathcal{N}$. Also set $F_j^{(n)} = F(ja,n)$. Then

$$\frac{dP_i}{dt} = -\sum_{j=0}^{\mathcal{N}} K_{ij}^{(n)} P_j, \quad \text{if } n(t) = n \qquad (3.5)$$

for $i = 0, \ldots, \mathcal{N}$. Away from the boundaries ($i \neq 0, \mathcal{N}$),

$$K_{ij}^{(n)} = \frac{1}{a}[\delta_{i,j-1} - \delta_{i,j}]F_j^{(n)}. \qquad (3.6)$$

One of the major benefits of the finite-difference scheme is that boundary conditions can be absorbed into the discrete operator $K_{ij}^{(n)}$, even when they are n-dependent. For the sake of illustration, consider the boundary conditions

$$P(0,t)1_{n(t)=1} = 0, \quad P(L,t)1_{n(t)=0} = 0, \qquad (3.7)$$

where $1_{n(t)=n}$ is the indicator function, which is equal to one if $n(t) = n$ and is zero otherwise. These boundary

conditions will apply to the example of a two-state gene network considered in section V. At the boundaries we require $P_0(t) = 0$ when $n = 1$ and $P_{\mathcal{N}}(t) = 0$ when $n = 0$. These conditions can be implemented by taking

$$K_{0j}^{(n)} = \frac{1}{a}\delta_{j,1}F_j^{(n)}, \quad K_{\mathcal{N}j}^{(n)} = -\frac{1}{a}\delta_{j,\mathcal{N}-1}F_j^{(n)}.$$

(Similarly, if each particle evolved according to an SDE rather than the ODE (3.1), then Eq. (3.2) would become a piecewise deterministic Fokker-Planck equation, and $K_{ij}^{(n)}$ would have an additional term consisting of a discrete Laplacian. It is well known from the theory of finite differences that Dirichlet of Neumann boundary conditions could be implemented by modifying the discrete Laplacian at the boundaries [1, 10], see Sect. VC.)

Let $\mathbf{P}(t) = (P_0(t), \ldots, P_{\mathcal{N}}(t))$ and introduce the probability density

$$\text{Prob}\{\mathbf{P}(t) \in (\mathbf{P}, \mathbf{P} + d\mathbf{P}), n(t) = n\} = \varrho_n(\mathbf{P}, t)d\mathbf{P}, \tag{3.8}$$

where we have dropped the explicit dependence on initial conditions. The resulting CK equation for the discretized piecewise deterministic PDE is [6, 7]

$$\frac{\partial \varrho_n}{\partial t} = \sum_{i=0}^{\mathcal{N}} \frac{\partial}{\partial P_i} \left[\left(\sum_{j=0}^{\mathcal{N}} K_{ij}^{(n)} P_j \right) \varrho_n(\mathbf{P}, t) \right] + \sum_{m=0,1} A_{nm}\varrho_m(\mathbf{P}, t) \tag{3.9}$$

with $A_{00} = -k_+ = -A_{10}$ and $A_{01} = k_- = -A_{11}$. Since the Liouville term in the CK equation is linear in $\mathbf{P}$, we can derive a closed set of equations for the moments of ϱ. For the sake of illustration, we will calculate the first and second moments. Let

$$V_{n,j}(t) = \mathbb{E}_\sigma[P_j(t)1_{n(t)=n}] = \int \varrho_n(\mathbf{P}, t)P_j(t)d\mathbf{P}, \tag{3.10}$$

where

$$\int f(\mathbf{P})d\mathbf{P} = \left[\prod_{j=0}^{\mathcal{N}} \int_0^\infty dP_j \right] f(\mathbf{P}).$$

Multiplying both sides of the CK equation (3.9) by $P_k(t)$ and integrating with respect to $\mathbf{P}$ gives (after integrating by parts and using $\varrho_n(\mathbf{P}, t) \to 0$ as $\mathbf{P} \to \infty$)

$$\frac{dV_{n,k}}{dt} = -\sum_{j=0}^{\mathcal{N}} K_{kj}^{(n)}V_{n,j} + \sum_{m=0,1} A_{nm}V_{m,k}.$$

We have assumed that the initial discrete state is distributed according to the stationary distribution of the matrix $\mathbf{A}$. If we now retake the continuum limit $a \to 0$, we obtain the CK equation

$$\frac{\partial V_n}{\partial t} = \left[-\frac{\partial}{\partial x}F(x, n) \right] V_n + \sum_{m=0,1} A_{nm}V_m, \tag{3.11}$$

with $V_n(x, t) = \mathbb{E}_\sigma[P(x, t)1_{n(t)=n}]$. The boundary conditions are $V_1(0, t) = 0 = V_0(L, t)$.

Next we consider the second-order moments

$$C_{n,kl}(t) = \mathbb{E}_\sigma[P_k(t)P_l(t)1_{n(t)=n}]$$
$$= \int \varrho_n(\mathbf{P}, t)P_k(t)P_l(t)d\mathbf{P}.$$

Multiplying both sides of the CK equation (3.9) by $P_k(t)P_l(t)$ and integrating with respect to $\mathbf{P}$ gives (after integration by parts)

$$\frac{dC_{n,kl}}{dt} = -\sum_{j=0}^{\mathcal{N}} K_{kj}^{(n)}C_{n,jl} - \sum_{j=0}^{\mathcal{N}} K_{lj}^{(n)}C_{n,jk} + \sum_{m=0,1} A_{nm}C_{m,kl}.$$

If we now retake the continuum limit $a \to 0$, we obtain a system of equations for the equal-time two-point correlations

$$C_n(x, y, t) = \mathbb{E}_\sigma[P(x, t)P(y, t)1_{n(t)=n}], \tag{3.12}$$

given by

$$\frac{\partial C_n}{\partial t} = -\frac{\partial}{\partial x}(F(x, n)C_n) - \frac{\partial}{\partial y}(F(y, n)C_n) + \sum_{m=0,1} A_{nm}C_m. \tag{3.13}$$

The boundary conditions are

$$C_1(0, y, t) = C_1(x, 0, t) = 0, \, C_0(L, y, t) = C_0(x, L, t) = 0.$$

Formally speaking, Eq. (3.11) for the first-order moments $V_n(x, t)$ is identical in form to the deterministic CK Eq. (2.10) for the single-particle probability density $p_n(x, t)$. Similarly, Eq. (3.13) for the second moment $C_n(x, y, t)$ is identical in form to the CK equation that would be written down for the joint probability density of two particles with positions x and y at time t. More generally, $C^{(r)}$ is related to the joint probability density of r particles. (The latter would correspond to having r particles in each of the boxes in Fig. 1(a).) However, these two representations are not equivalent, particularly in the case of bounded domains [10]. From a physical perspective, there is a much wider class of boundary conditions that one can impose on the SPDE (3.2) compared to the SDE (2.3) or its finite particle extension (3.1). This reflects the fact that particle conservation needn't hold at the SPDE level. For example, if $x \in [0, L]$ then one could impose an inhomogeneous boundary condition at $x = L$, say, of the form $\sum_n F(L, n)P_n(L, t) = \eta$. One final observation is that solutions to Eq. (3.13) are generally not separable, that is, $C_n(x, y, t) \neq V_n(x, t)V_n(y, t)$. In other words, Eq. (3.4) holds. This reflects the fact that, although the particles are non-interacting, they are all moving under the same single realization of the DMNP (common environmental noise) and this induces statistical correlations in the "distribution" of densities $P(x, t)$ with respect to different realizations of the DMNP.

IV. EXAMPLE: VELOCITY JUMP PROCESS

A. Single particle perspective

As a first illustration of the above analysis, consider the velocity jump process

$$\frac{dx}{dt} = [v_+ + v_-]n(t) - v_-, \quad k_\pm = k.$$

The corresponding CK equation (2.10) reduces to

$$\frac{\partial p_0}{\partial t} = v_- \frac{\partial p_0}{\partial x} + k[p_1 - p_0] \quad (4.1a)$$

$$\frac{\partial p_1}{\partial t} = -v_+ \frac{\partial p_1}{\partial x} + k[p_0 - p_1]. \quad (4.1b)$$

First suppose that $x \in \mathbb{R}$ and $v_+ = v_- = v$. The marginal probability density $p(x,t) = p_0(x,t) + p_1(x,t)$ then sat-

isfies the telegrapher's equation [16, 17]

$$\left[\frac{\partial^2}{\partial t^2} + 2k \frac{\partial}{\partial t} - v^2 \frac{\partial^2}{\partial x^2} \right] p(x,t) = 0. \quad (4.2)$$

(The individual densities $p_{0,1}$ satisfy the same equations.) The telegrapher's equation can be solved explicitly for a variety of initial conditions. More generally, the short-time behavior (for $t \ll \tau_c = 1/2k$) is characterized by wave-like propagation with $\langle x(t) \rangle^2 \sim (Vt)^2$, whereas the long-time behavior ($t \gg \tau_c$) is diffusive with $\langle x^2(t) \rangle \sim 2Dt$, $D = v^2/2k$. As an explicit example, the solution for the initial conditions $p(x,0) = \delta(x)$ and $\partial_t p(x,0) = 0$ is given by

$$p(x,t) = \frac{e^{-kt}}{2}[\delta(x - vt) + \delta(x + vt)] + \frac{ke^{-kt}}{2v}\left[I_0(k\sqrt{t^2 - x^2/v^2}) + \frac{t}{\sqrt{t^2 - x^2/v^2}} I_0(k\sqrt{t^2 - x^2/v^2}) \right]$$

$$\times [\Theta(x + vt) - \Theta(x - vt)],$$

where I_n is the modified Bessel function of n-th order and Θ is the Heaviside function. The first two terms clearly represent the ballistic propagation of the initial data along characteristics $x = \pm vt$, whereas the Bessel function terms asymptotically approach Gaussians in the large time limit. The steady-state equation for $p(x)$ is simply $p''(x) = 0$, which from integrability means that $p(x) = 0$ point-wise. This is consistent with the observation that the above explicit solution satisfies $p(x,t) \to 0$ as $t \to \infty$.

A non-trivial steady-state solution can be obtained on the semi-infinite line, $x > 0$, for $v_+ \neq v_-$. One example of such a system is the Dogterom-Leibler model of microtubule catastrophes [18, 19], in which microtubules switch between growth and shrinkage phases at a rate k, with $v_\pm$ the corresponding elongation and shrinkage velocities. We can determine a condition for the existence of a steady-state solution by adding equations (4.1a) and (4.1b) and setting $\partial_t p_{0,1} = 0$. This gives $v_+ p_1'(x) - v_- p_0'(x) = 0$, and thus $v_+ p_1(x) - v_- p_0(x) = $ constant. Normalizability of $p_{0,1}(x)$ implies that the constant must be zero and, hence, $p_1(x) = P(x)/v_+, p_0(x) = P(x)/v_-$ with P satisfying the equation

$$\frac{dP(x)}{dx} = \left[\frac{k}{v_-} - \frac{k}{v_+} \right] P(x) = -\frac{V}{D} P(x),$$

where $V = (v_- - v_+)/2$ and $D = (v_+ v_-)/2k$ is an effective diffusivity. It immediately follows that there exists a steady-state solution, $P(x) = P(0)e^{-Vx/D}$, $0 < x < \infty$,

if and only if $V > 0$. In the regime $V < 0$, catastrophe events are relatively rare and the microtubule continuously grows with mean speed $|V|$, whereas, for $V > 0$ the catastrophe events occur much more frequently so that there is a balance between growth and shrinkage that results in a steady-state distribution of microtubule lengths.

B. SPDE perspective

Turning to the corresponding stochastic Liouville equation (3.2), we can identify the first moments V_n with the solutions p_n of Eq. (4.1), whereas the second order moments $C_n(x,y,t)$ satisfy

$$\frac{\partial C_0}{\partial t} = v_- \frac{\partial C_0}{\partial x} + v_- \frac{\partial C_0}{\partial y} + k[C_1 - C_0] \quad (4.3a)$$

$$\frac{\partial C_1}{\partial t} = -v_+ \frac{\partial C_1}{\partial x} - v_+ \frac{\partial C_1}{\partial y} + k[C_0 - C_1]. \quad (4.3b)$$

Again let us first consider the case $(x,y) \in \mathbb{R}^2$ and $v_+ = v_- = v$. Adding and subtracting Eqs. (4.3a) and Eqs. (4.3b), and setting $C = C_1 + C_0$, $\widehat{C} = C_1 - C_0$ yields

$$\frac{\partial C}{\partial t} = -v \frac{\partial \widehat{C}}{\partial x} - v \frac{\widehat{C}}{\partial y} \quad (4.4a)$$

$$\frac{\partial \widehat{C}}{\partial t} = -v \frac{\partial C}{\partial x} - v \frac{\partial C}{\partial y} - 2k\widehat{C}. \quad (4.4b)$$

Differentiating Eq. (4.4a) with respect to t and using Eq. (4.4b) establishes that C satisfies the 2D PDE

$$\left[\frac{\partial^2}{\partial t^2} + 2k\frac{\partial}{\partial t} - v^2\left(\frac{\partial}{\partial x} + \frac{\partial}{\partial y}\right)^2\right]C(x,y,t) = 0. \quad (4.5)$$

This PDE is clearly not separable, which implies that $C(x,y,t) \neq p(x,t)p(y,t)$. If the cross-differentiation term $2v^2\partial_x\partial_y$ were absent from Eq. (4.5), then would be identical to the 2D version of the telegrapher's equation. Even for this simpler PDE, it is necessary to resort to numerical methods in order to solve the initial value problem. Note, however, that $C(x,y,t) \to 0$ in the limit $t \to 0$.

Now suppose $x > 0$, $y > 0$ and $v_+ < v_-$. Adding Eqs. (4.3a) and (4.3b) then yields

$$\frac{\partial\phi(x,y)}{\partial x} + \frac{\partial\phi(x,y)}{\partial y} = 0, \quad x,y > 0$$

with $\phi(x,y) = v_+C_1(x,y) - v_-C_0(x,y)$. It follows that $\phi(x,y) = \Phi(x-y)$ for some function Φ and, hence,

$$C_0(x,y) = \frac{P(x+y)}{v_-} + \Psi_0(x-y),$$

$$C_1(x,y) = \frac{P(x+y)}{v_+} + \Psi_1(x-y)$$

with $v_+\Psi_1 - v_-\Psi_0 = \Phi$. Substituting into the steady-state version of Eq. (4.3a) shows that $\Psi_0 = \Psi_1 = \Psi$, say, and

$$\frac{\partial P}{\partial x} + \frac{\partial P}{\partial y} = -\frac{V}{D}P. \quad (4.6)$$

The latter has the solution $P(z) = P(0)e^{-Vz/D}$ with $z = x + y$. Finally, integrability of the solutions and the integral identities

$$\int_0^\infty C_n(x,y)dx = V_n(y), \quad \int_0^\infty C_n(x,y)dy = V_n(x) \quad (4.7)$$

require $\Psi = 0$ so that

$$C_n(x,y) = C_n(0)e^{-V(x+y)/D} = V_n(x)V_n(y). \quad (4.8)$$

This establishes that in steady-state the two-point correlations disappear for the given velocity jump process.

V. EXAMPLE: TWO-STATE GENE NETWORK

A. Single-particle perspective

In order to further illustrate the occurrence of statistical correlations in a population of particles driven by a common DMNP, consider the simple two-state model of gene regulation shown in Fig. 3. The gene randomly switches between an inactive state I (no protein production) and an active state A where proteins are produced at a rate r. Proteins subsequently degrade at a rate γ. (The stages of transcription and translation are lumped together so we do not keep track of the amount of mRNA.) The corresponding reaction scheme is

$$I \underset{k_-}{\overset{k_+}{\rightleftharpoons}} A \xrightarrow{r} \text{p} \xrightarrow{\gamma} \emptyset,$$
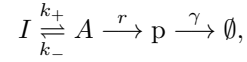
where $k_\pm$ are the switching rates between the inactive and active states. Suppose that the number of proteins is sufficiently large so that we can represent the dynamics in terms of a continuous-valued protein concentration $x(t)$. Let $n(t)$ denote the current state of the gene with $n(t) = 0$ if it is inactive and $n(t) = 1$ if it is active. The protein evolves according to the piecewise-deterministic equation

$$\frac{dx}{dt} = rn - \gamma x, \quad (5.1)$$

for $n(t) = n \in \{0,1\}$. Eq. (5.1) has the form of Eq. (2.3) with

$$F(x,0) = -\gamma x, \quad F(x,1) = r - \gamma x.$$

Note that $x(t)$ can be restricted to the closed interval $\Sigma = [0, r/\gamma]$ where $F(x,0) < 0$ and $F(x,1) > 0$ within the interior of the domain.

Several previous studies of two-state regulatory networks have focused on properties of the steady-state probability density [20–24] by solving the time-independent version of the CK equation (2.10) with the boundary conditions (3.7) and $L = r/\gamma$. More specifically adding Eqs. (2.10a) and (2.10b), and setting time derivatives to zero yields

$$\frac{\partial}{\partial x}(F(x,0)p_0(x)) + \frac{\partial}{\partial x}(F(x,1)p_1(x)) = 0,$$

that is, $F(x,0)p_0(x) + F(x,1)p_1(x) = c$ for some constant c. The reflecting boundary conditions imply that $c = 0$.
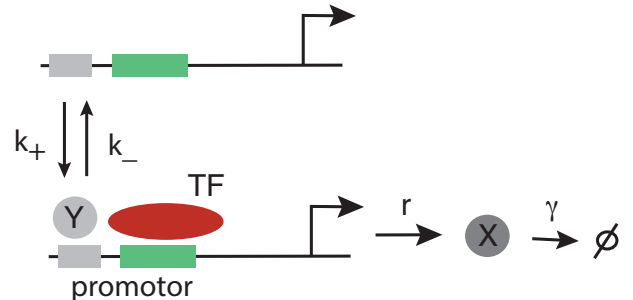
FIG. 3. [Color online] A gene randomly switches between an on-state and an off-state at rates $k_\pm$ due to the binding/unbinding of a transcription factor (TF) to a promotor site. In the on-state proteins are produced at a rate r and degrade at a rate γ. (For simplicity, the intermediate transcription step of producing mRNA is ignored.)

Since $F(x,n)$ is non-zero for all $x \in \Sigma$, we can express $p_1(x)$ in terms of $p_0(x)$: $p_1(x) = -F(x,0)p_0(x)/F(x,1)$. Substituting into Eq. (2.10a) yields the solutions

$$p_n(x) = \frac{1}{Z_N|F(x,n)|}$$
$$\times \exp\left(-\int_0^x \left(\frac{k_+}{F(z,1)} + \frac{k_-}{F(z,0)}\right)dz\right). \tag{5.2}$$

where Z_n is a normalization factor (assuming it exists). Given the no-flux boundary conditions, we can impose the normalization condition $\int_0^L[p_0(x)+p_1(x)]dx = 1$. Integrating the steady-state versions of Eqs. (2.10) with respect to x then shows that

$$\int_0^L p_0(x)dx = \frac{k_-}{k_-+k_+}, \quad \int_0^L p_1(x)dx = \frac{k_+}{k_-+k_+}.$$

For the particular example of the twos-tate regulatory network one thus finds [21]

$$p_0(x) = C\,(\gamma x)^{-1+k_+/\gamma}(r-\gamma x)^{k_-/\gamma}, \tag{5.3a}$$
$$p_1(x) = C\,(\gamma x)^{k_+/\gamma}(r-\gamma x)^{-1+k_-/\gamma} \tag{5.3b}$$

for $C = \gamma\left[r^{(k_++k_-)/\gamma}B(k_+/\gamma,k_-/\gamma)\right]^{-1}$, where $B(\alpha,\beta)$ is the Beta function $B(\alpha,\beta) = \int_0^1 t^{\alpha-1}(1-t)^{\beta-1}dt$. In
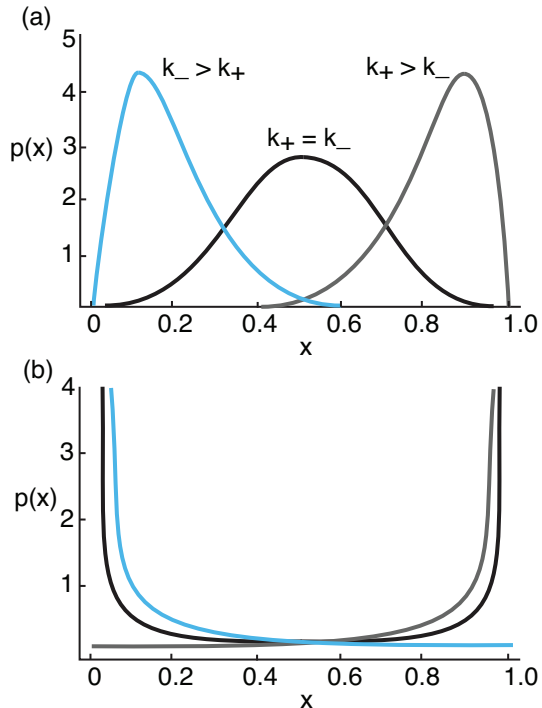

(a)

(b)

FIG. 4. [Color online] Sketch of steady-state protein density $p(x)$ for a simple regulated network in which the promoter transitions between an active and inactive state at rates $k_\pm$. (a) Case $k_\pm/\gamma > 1$: there is a graded density that is biased towards $x = 0, 1$ depending on the ratio k_+/k_-. (b) Case $k_\pm/\gamma < 1$: there is a binary density that is concentrated around $x = 0, 1$ depending on the ratio k_+/k_-

Fig. 4, we sketch $p(x) = p_0(x) + p_1(x)$ for various values of $K_\pm = k_\pm/\gamma$. It can be seen that if the rates $k_\pm$ of switching between the active and inactive gene states are faster than the rate of degradation γ then the steady-state density is unimodal (graded), whereas if the rate of degradation is faster then the density tends to be concentrated around $x = 0$ or $x = 1$, consistent with a binary process. (The density actually diverges at both ends but if $k_+ \gg k_-$ or vice versa, then the associated boundary layer is infinitesimal.)

B. SPDE perspective

Let us now consider the above example from the SPDE perspective, where we imagine a large population of non-interacting gene networks driven by a common noise source. That is, we assume there is some common environmental stimulus that simultaneously controls the activation and inactivation of the gene across a population of cells [23, 24]. The discrete environmental states could represent the presence of some extracellular metabolite or signaling molecule, perhaps arising from changes in the physiological or hormonal state that a cell experiences in a multicellular organism. Since we can identify the steady-state solution $p_n(x)$ with the first moment $\lim_{t\to\infty}\mathbb{E}_\sigma[P(x)]$, we will consider the second-order moments $C_n(x,y)$, $n = 0, 1$.

The steady-state version of Eq. (3.13) becomes

$$-\frac{\partial}{\partial x}[\gamma x C_0] - \frac{\partial}{\partial y}[\gamma y C_0] = k_- p_1 - k_+ p_0, \tag{5.4a}$$

$$\frac{\partial}{\partial x}[(r-\gamma x)C_1] + \frac{\partial}{\partial y}[(r-\gamma y)C_1] = -k_- p_1 + k_+ p_0. \tag{5.4b}$$

These are supplemented by the integral identities

$$\int_R C_0(x,y)dx\,dy = \frac{k_-}{k_-+k_+}, \quad \int_R C_1(x,y)dx\,dy = \frac{k_+}{k_-+k_+},$$

where $A = [0,r/\gamma] \times [0,r/\gamma]$. The quasilinear Eqs. (5.4) are similar in form to the CK equations for the first moments of a two-stage model of mRNA and protein concentrations, see section V.C and Ref. [23]. As noted in Ref. [23], it is difficult to find analytic solutions to these equations so that one has to use numerical simulations. Here we show how the method of characteristics may be used to extract some information about the asymptotic behavior of the variances.

First, rewrite Eqs. (5.4) tin the matrix form

$$\mathbf{M}(x)\frac{\partial \mathbf{C}(x,y)}{\partial x} + \mathbf{M}(y)\frac{\partial \mathbf{C}(x,y)}{\partial y} = \mathcal{F}, \tag{5.5}$$

with $\mathbf{C} = (C_0, C_1)^\top$, $\mathcal{F} = (\mathcal{F}_0, \mathcal{F}_1)^\top$ for

$$\mathcal{F}_0 = (2\gamma - k_+)C_0 + k_- C_1, \quad \mathcal{F}_1 = k_+ C_0 + (2\gamma - k_-)C_1,$$

and $\mathbf{M}(x) = \text{diag}(F(x,0), F(x,1))$. Hence, Eq. (5.5) can be analyzed using the method of characteristics [25]. Let

$\Sigma_2 = [0, r/\gamma] \times [0, r/\gamma] \subset \mathbb{R}^2$. Away from the boundary $\partial\Sigma_2$ we have a hyperbolic system with a pair of real characteristics for all $0 < x < r/\gamma$, $0 < y < r/\gamma$. The slope $dy/dx = \lambda$ of a characteristic is determined from the equation $\det[\mathbf{M}(y) - \lambda\mathbf{M}(x)] = 0$, which yields

$$\lambda_1 = \frac{F(y,0)}{F(x,0)} = \frac{y}{x}, \quad \lambda_2 = \frac{F(y,1)}{F(x,1)} = \frac{r - \gamma y}{r - \gamma x}. \quad (5.6)$$

The corresponding characteristic curves are

$$y = y_0(x) = ax, \quad y = y_1(x) = bx + \frac{r}{\gamma}(1 - b) \quad (5.7)$$

for constants a, b. The corresponding eigenvectors are $\sigma_1 = (1,0)^\top, \sigma_2 = (0,1)^\top$. The curves are plotted in Fig. 5. It can be seen that each point (x, y) in the interior of the domain Σ_2 is at the intersection of a unique pair of characteristics propagating from the boundaries.

In particular, one has the following equations for $\mathbf{C}$ along the characteristics $y = y_j(x)$ [25],

$$\sigma_j^\top \mathbf{M}(x)\left(\frac{\partial\mathbf{C}}{\partial x} + \lambda_j\frac{\partial\mathbf{C}}{\partial y}\right) = \sigma_j^\top \mathcal{F}, \quad j = 1, 2. \quad (5.8)$$

For the given system we have the pair of equations

$$-\gamma x\frac{dC_0}{dx} = k_-C_1 + (2\gamma - k_+)C_0, \quad y = y_0(x) \quad (5.9a)$$
$$(r - \gamma x)\frac{dC_1}{dx} = k_+C_0 + (2\gamma - k_-)C_1, \quad y = y_1(x). \quad (5.9b)$$

Integrating Eqs. (5.9a,b) with respect to x and imposing the boundary conditions gives

$$C_0(x, ax) = \frac{k_-}{\gamma}x^{-2+k_+/\gamma} \quad (5.10a)$$
$$\times\left[\frac{A_0}{x_0^{-2+k_+/\gamma}} - \int_{x_0}^x \frac{C_1(x', ax')}{[x']^{-1+k_+/\gamma}}dx'\right],$$

$$C_1(x, y_1(x)) = \frac{k_+}{\gamma}(r/\gamma - x)^{-2+k_-/\gamma} \quad (5.10b)$$
$$\times\left[\frac{A_1}{[r/\gamma - x_0]^{-2+k_-/\gamma}} + \int_{x_0}^x \frac{C_0(x', y_1(x'))}{[r/\gamma - x']^{-1+k_-/\gamma}}dx'\right]$$

for $0 < x_0 < r/\gamma$ and constants A_0, A_1.

The above pair of equations allow us to determine the asymptotic behavior of the variances $\sigma_n^2(x) = C_n(x, x)$. For the sake of illustration, consider the case of graded responses for which $k_\pm/\gamma > 1$. Setting $a = 1, b = 1$ and taking the limits $x \to 0$ in Eq. (5.10a) and $x \to r/\gamma$ in Eq. (5.10b) shows that

$$\sigma_0^2(x) \sim x^{-2+k_+/\gamma}, \quad x \sim 0,$$
$$\sigma_1^2(x) \sim [r - \gamma x]^{-2+k_-/\gamma}, \quad x \sim r/\gamma,$$

We have used the fact that the integral terms are clearly finite for the graded response. It follows that in the
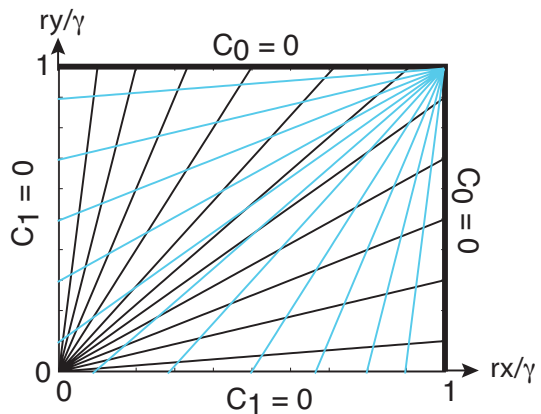

FIG. 5. [Color online] Characteristic curves for $\lambda_1 = y/x$ (dark) and $\lambda_2 = (r - \gamma y)/(r - \gamma x)$ (light).

graded response regime, the variances have removable singularities at the boundaries $x = 0, r/\gamma$ whenever $1 < k_\pm/\gamma < 2$.

It is clear from the above analysis that $C_n(x, y) \neq V_n(x)V_n(y)$, thus providing an explicit example of statistical correlations at the population level. Moreover, such correlations could be experimentally measurable. That is, one could imagine labeling the protein product within each cell using green fluorescent protein (GFP) and taking a snapshot of the GFP intensities across the population at some time t, after being exposed to a single realization of the environment. The resulting histogram of GFP intensities would yield an approximation to $P(x, t)$ for the given realization. Repeating this for multiple runs would yield different realizations of the stochastic density $P(x, t)$ from which statistical correlations of the population density could be constructed. This procedure is distinct from most studies of gene networks, which tend to focus on moments of $P(x, t)$ averaged with respect to different realizations of the environment, that is, $\int x^k \mathbb{E}_\sigma[P(x, t)]dx$ rather than $\mathbb{E}_\sigma[P(x_1, t)\cdots P(x_k, t)]$.

C. Extensions of gene network model

The above two-state gene network is about the simplest gene regulatory network that one could write down. A more realistic model would need to include the dynamics of mRNA, allow for the possibility of nonlinear regulatory feedback, and also need to take into account the effects of intrinsic noise. The latter arises from a number of different sources, including fluctuations in the binding or unbinding of the TF to or from the promotor site and demographic noise associated with a finite number of proteins [24]. All of these features can be incorporated into our SPDE framework. In particular, our derivation of the moment equations for the stochastic Liouville equation (3.2) did not require the functions $F(x, n)$ to be linear, nor the number of discrete states n

be restricted to two. However, as we found for even the simple two-state gene network with linear $F(x,n)$, analysis of the resulting system of PDEs for the second moments is non-trivial. Therefore, in most cases one would have to compare the observed statistics with a numerical solution of the corresponding PDEs. Here we outline a few possible extensions in a little more detail.

Intrinsic noise

The two-state environmental switching model has recently been extended to include the effects of molecular noise and nonlinearities by carrying out a system-size expansion of the master equation for protein synthesis when the environment is in state n [24] (see also Ref. [26]). This leads to a modification of the SDE (2.3) of the form

$$dX(t) = F(X, n(t))dt + \sqrt{\frac{\sigma(X, n(t))}{\Omega}}dW(t), \quad (5.11)$$

for $n(t) \in \{0, 1\}$, where Ω is the system size (such as the expected number of proteins), $W(t)$ is a Wiener process with

$$\langle dW(t) \rangle = 0, \quad \langle dW(t)dW(t') \rangle = \delta(t - t')dt\,dt',$$

and $\sigma(X, n)$ is a noise intensity that typically depends on both the protein concentration and the state of the environment. Eq. (5.11) is in the form of a piecewise SPDE, whose associated CK equation for the probability densities $p_n(x, t)$ is

$$\frac{\partial p_n}{\partial t} = \left[-\frac{\partial}{\partial x}F(x, n) \right] p_n + \frac{1}{2\Omega}\left[\frac{\partial^2 \sigma^2(x, n)}{\partial x^2} \right] p_n$$
$$+ \sum_{m=0,1} A_{nm}p_m \quad (5.12)$$

for $n = 0, 1$. The intrinsic multiplicative noise is treated in the Ito sense. Hufton *et al.* [24] analyzed the model from a particle perspective and showed how to approximate the steady-state solutions of Eq. (5.12) by carrying out a linear noise approximation, which can be applied even when F, σ and $k_\pm$ are nonlinear functions of x.

Here we briefly indicate how the model can be formulated from the SPDE perspective. Consider a large population of non-interacting cells labeled by $\ell = 1, \ldots, \mathcal{M}$ with protein concentrations $X_\ell(t)$, all being driven by the same external or environmental variable $n(t)$. Eq. (3.1) becomes

$$dX_\ell = F(X_\ell, n(t))dt + \sqrt{\frac{\sigma(X_\ell, n(t))}{\Omega}}dW_\ell(t) \quad (5.13)$$

for $\ell = 1, \ldots, \mathcal{M}$, with the stochastic variable $n(t)$ independent of ℓ and evolving according to the continuous Markov chain with generator $\mathbf{A}$ given by Eq. (2.5). The important point to note is that the intrinsic noise within each cell is described by an independent Wiener process

$$\langle dW_\ell(t) \rangle = 0, \quad \langle dW_\ell(t)dW_{\ell'}(t') \rangle = \delta_{\ell,\ell'}\delta(t - t')dt\,dt'.$$

As in section III, take the thermodynamic limit $\mathcal{M} \to \infty$, and let $P(x, t)$ denote the density of particles in state x at time t given a particular realization of the DMNP. The stochastic Liouville equation (3.2) is replaced by the stochastic FPE

$$\frac{\partial}{\partial t}P(x, t) = \left[-\frac{\partial}{\partial x}F(x, n(t)) \right] P(x, t)$$
$$+ \frac{1}{2\Omega}\left[\frac{\partial^2 \sigma^2(x, n(t))}{\partial x^2} \right] P(x, t). \quad (5.14)$$

One can now derive moment equations along analogous lines to section III and Ref. [1].

Two-stage model of mRNA and protein concentrations

As highlighted in Ref. [23], it is straightforward to write down a two-stage version of the two-state gene network model (5.1) that incorporates the production and decay of mRNA. Let $x(t)$ denote the concentration of protein and $u(t)$ the concentration of mRNA. The corresponding system of kinetic Eqs. at the single gene level are given by

$$\frac{dx}{dt} = r_p u - \gamma_p x, \quad \frac{du}{dt} = rn(t) - \gamma_u u(t) \quad (5.15)$$

for $n(t) = n \in \{0, 1\}$. Here γ_p, γ_u are the degradation rates of protein and mRNA, r_p is the environment-independent rate at which protein is translated from active mRNA and r is the rate of mRNA synthesis when the gene is active. Let $p_n(x, y, t)$ be the probability density for the joint process. The associated CK equations are [23]

$$\frac{\partial p_0}{\partial t} = -\frac{\partial}{\partial x}[(r_p u - \gamma_p x)p_0] - \frac{\partial}{\partial u}[-\gamma_u u)p_0]$$
$$+ k_- p_1 - k_+ p_0, \quad (5.16a)$$
$$\frac{\partial p_1}{\partial t} = -\frac{\partial}{\partial x}[(r_p u - \gamma_p x)p_1] - \frac{\partial}{\partial u}[(r - \gamma_u u)p_1]$$
$$- k_- p_1 + k_+ p_0. \quad (5.16b)$$

The steady-state version of these equations is similar in form to Eqs. (5.4). However, the latter determine the second-order moments of the one-stage model in the SPDE perspective, whereas the former represent the particle perspective of the two-state model, or equivalently the first-order moments equations of the SPDE perspective; the second-order moment equations would involve four independent variables.

VI. DISCUSSION

In this paper we extended our recent work on SDEs in random environments [1] by considering a large population of non-interacting particles evolving according to

to piecewise deterministic dynamics in the presence of global dichotomous noise. Such a system could represent the switching on and off of genes in a population of cells driven by a common environmental stimulus. We highlighted the difference between the standard approach to analyzing dichotomous noise, which we call the particle perspective, and the SPDE perspective. The former simultaneously considers realizations of the piecewise deterministic dynamics and the DMNP, which results in a deterministic CK equation, whereas the latter considers multiple realizations of the piecewise dynamics for a single realization of the environmental noise, which leads to a stochastic Liouville equation. A relationship between the particle and SPDE perspectives was obtained by deriving moment equations for the distribution of the resulting stochastic population density by averaging over multiple realizations of the environment. We illustrated the theory by considering two simple examples of dichotomous flows, a velocity jump process and a two-state gene regulatory network. In both cases we showed how the global environmental input induces statistical correlations between different realizations of the population density.

In the probability literature, a particle driven by a DMNP is an example of a much more general type of stochastic process known as a piecewise deterministic Markov process (PDMP). That is, $x(t)$ could belong to a higher-dimensional space, $n(t)$ could take on more than two discrete values, and most significantly, the transition rates of the discrete Markov process could themselves depend on the continuous variable. For example, the switching on or off of a gene could depend on the concentration of its protein product (regulatory feedback) or the opening and closing of an ion channel could be voltage-gated. A rigorous introduction to PDMPs can be found in Refs. [27–30]. Note that a major assumption of the SPDE formulation is that the switching rates $k_\pm$ of the environment are independent of the states of the individual particles. This is necessary otherwise we could not separate the realizations of the different particle trajectories and the realizations of the dichotomous noise. It also allows us to interpret the discretized piecewise deterministic equation (3.9) as a CK equation, and to derive the closed set of moment equations. One way to extend the model would be to take the switching rates to depend on some collective population variable such as the population mean $X = \mathcal{M}^{-1} \sum_{\ell=1}^{\mathcal{M}} x_\ell$. (In applications to collective cell signaling, for example, it is possible that the protein produced by the cells could be secreted into the environment and thus influence the state of the environment. A classical example is bacterial quorum sensing [31].) In the thermodynamic limit, we would have $X(t) = \int_\Sigma x P(x,t) dx$ and thus the switching rates would be functionals of $P(x,t)$. Now carrying out the discretization scheme in Sect. IIIA would lead to a CK equation of the form (3.9), except that the matrix $\mathbf{A}$ would now depend on the vector $\mathbf{P}$. Although we could still construct moment equations, the resulting nonlinearities would result in a moment closure problem.

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