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A STOCHASTIC HYBRID FRAMEWORK FOR OBTAINING STATISTICS OF MANY RANDOM WALKERS IN A SWITCHING ENVIRONMENT*

ETHAN LEVIEN† AND PAUL C. BRESSLOFF†

Abstract. We analyze a population of randomly walking particles in a stochastically switching environment by formulating the model as a stochastic hybrid system. The latter describes the evolution of the probability distribution of the particles, which is a random variable depending on realizations of the random environment. We derive a hierarchy of moment equations for the probability distribution, which allows us to extract statistics of the multiparticle system. As a specific example, we consider a population of particles walking on a one-dimensional lattice with a dynamic gate at some unknown location, which stochastically switches between an open and closed state according to a two-state Markov process. This type of model has two levels of stochasticity: one due to the jump process describing the evolution of each particle on the lattice, and the other due to the switching of the gate. By solving the moment equations for the stochastic hybrid system, we extract statistical information about the location and dynamics of the gate in terms of how the mean and variance of site occupancies varies with distance of a given site from the gate. This has potential applications in the analysis of time series data obtained from biophysical experiments on the diffusion of particles in the plasma membrane of cells.

Key words. birth-death processes, stochastic hybrid systems, diffusion, cell biology

AMS subject classifications. 82C31, 92C37, 34F05

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1. Introduction.

A random walk with spatially varying jump rates on a spatially discrete lattice can be viewed as a birth-death process (BDP), which is an example of a continuous-time Markov process. The defining feature of a BDP is that jumps can only occur between neighboring lattice states. They are a fundamental component of numerous mathematical models in fields ranging from population and cell biology [1, 3, 25] to queueing theory and operations research [15]. The theory of BDPs is typically developed under the assumption that the birth and death rates, α and β, are independent of time (homogeneous BDPs), although there have been several studies involving time-dependent transition rates (inhomogeneous BDPs); see for example [33, 12]. In this paper, we consider another level of complexity whereby the transition rates are themselves stochastic. This is primarily motived by the example of diffusion of proteins in the cell membrane, although the theory developed is more general, having applications in gene networks, queuing theory, and population biology.

At the simplest level, the plasma membrane can be treated as a two-dimensional sheet of membrane lipids into which proteins are embedded. *Membrane lipids* are a group of compounds (structurally similar to fats and oils) which form the double-layered surface of all cells. Lipids are amphiphilic: they have one end that is soluble in water ("polar") and another end that is soluble in fat ("nonpolar"). By forming a

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†Department of Mathematics, University of Utah, Salt Lake City, UT 84112 (levien@math.utah.edu, bressloff@math.utah.edu).

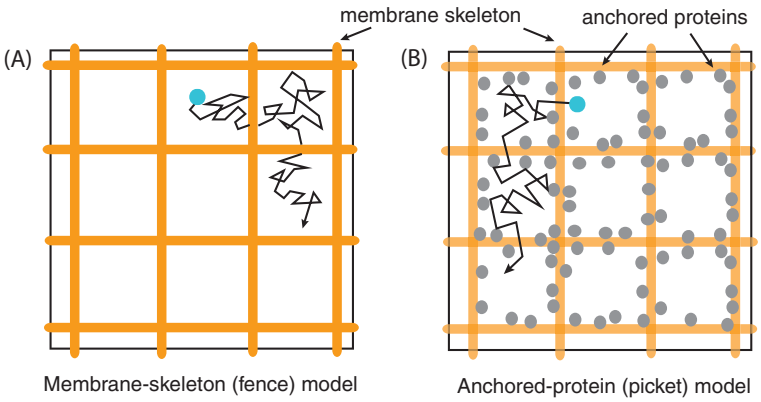

FIG. 1. *Picket-fence model of membrane diffusion. The plasma membrane is parceled up into compartments whereby both transmembrane proteins and lipids undergo short-term confined diffusion within a compartment and long-term hop diffusion between compartments. This corralling is assumed to occur by two mechanisms.* (A) *The membrane-cytoskeleton (fence) model: transmembrane proteins are confined within the mesh of the actin-based membrane skeleton.* (B) *The anchored-protein (picket) model: transmembrane proteins, anchored to the actin-based cytoskeleton, effectively act as rows of pickets along the actin fences.*

double layer with the polar ends pointing outwards and the nonpolar ends pointing inwards, membrane lipids can form a "lipid bilayer" which keeps the watery interior of the cell separate from the watery exterior. In the *fluid mosaic model* of [29], the membrane lipids are treated as the solvent (water concentrations are very low within the membrane) into which proteins are dissolved. Although the diffusion of lipids appears to be Brownian in pure lipid bilayers, single-particle tracking experiments indicate that lipids and proteins undergo periods of confined diffusion, in which the mean-square displacement is sublinear in time. Confinement domains arise due to the fact that the cell membrane is a highly heterogeneous, fluctuating environment, in which obstacles can appear and disappear stochastically [27, 22]. This has led to a modification of the original fluid mosaic model, in which lipids and transmembrane proteins undergo confined diffusion within, and hop between, membrane microdomains or corrals [32, 22, 23]; the corraling could be due to "fencing" by the actin cytoskeleton or confinement by anchored-protein "pickets"; see Figure 1. Partitioning the membrane into a set of corrals implies that anomalous subdiffusion of proteins will be observed on intermediate timescales, due to the combined effects of confinement and binding to the actin cytoskeleton. However, on timescales over which multiple hopping events occur, normal diffusion will be recovered. A rough estimate of the corresponding diffusion coefficient is $D \sim L^2/\tau$, where L is the average size of a microdomain and τ is the mean hopping rate between microdomains. A typical range of values for various types of mammalian cell are $L \sim 30-240$ nm and $\tau \sim 1-20$ ms.

Brown et al. [8] modeled the flux of proteins into and out of a well-mixed confinement domain in terms of a stochastically gated BDP. The authors focused on the particular problem of determining whether or not there is a dynamic gate based on time series data from a population of particles within the gated domain. They analyzed the system as a rate process with dynamic disorder using the framework developed in [34], and derived analytical expressions for the mean and variance of the number of particles in the domain. This model was later extended in order to study protein trafficking in dendritic spines [7]. A natural generalization of the model studied by

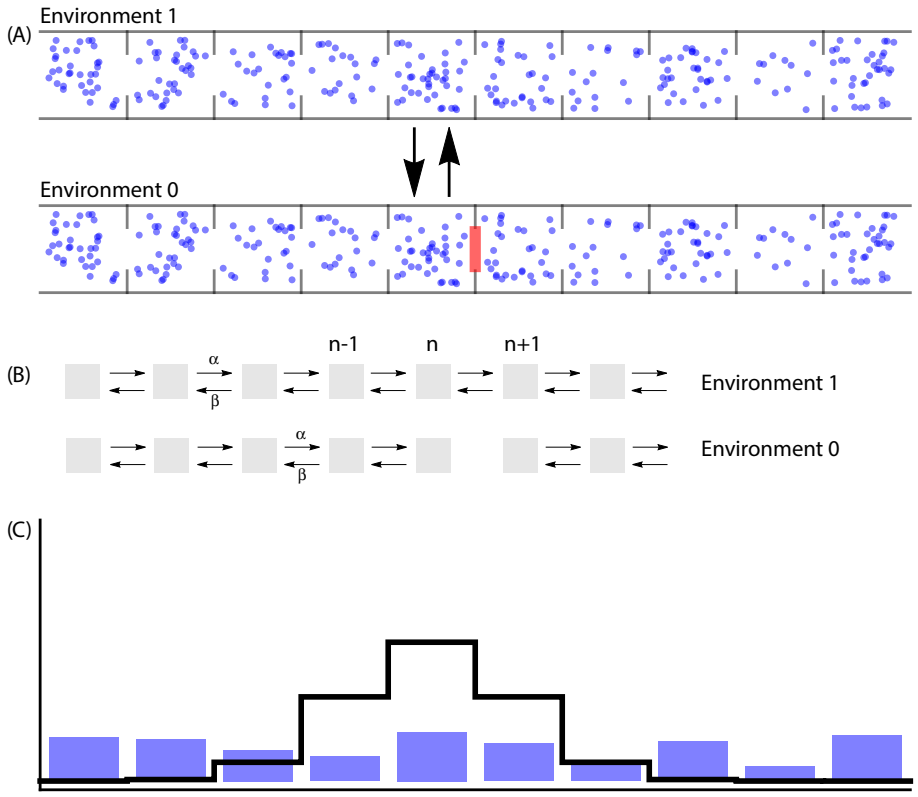

FIG. 2. *A diagram depicting the two scales of stochasticity for a set of well-mixed confinement domains with nearest-neighbor diffusive coupling arranged along a one-dimensional lattice. (Since the individual compartments are well-mixed, we can ignore the spatial structure of each compartment and just keep track of site occupancies. Particles then simply hop between neighboring sites.)* (A) *A large population of particles diffusing in a dynamic random environment that can be in one of two states due to the presence of a dynamic gate. In state* 1 *the gate is open and particles can freely diffuse between each well-mixed confinement domain (lattice site), while in state* 0 *the gate is closed (indicated by the shaded rectangle) and particles are blocked from diffusing between two neighboring sites.* (B) *The stochastic position of each particle on the lattice is described by a BDP whose transition matrix randomly switches between two forms due to the switching environment. The population of particles is described by an ensemble of noninteracting BDPs driven by a common environmental input (state of the dynamic gate).* (C) *Histograms comparing the probability distributions* $P(n,t)$ *(bars) for a single realization of the random environment in* (A) *and* $p(n,s,t)$ *(black line) obtained by averaging over multiple realizations of the environment. The difference is due to the effects of the dynamic environment concentrating particles to the left and right of the gate, an effect that would be smoothed out if we averaged over multiple realizations.*

Brown et al. consists of a population of particles jumping along a sequence of confinement domains whose connections may be gated; see Figure 2 (A). If the domains are well-mixed, then one can represent each domain as a site on a one-dimensional lattice, and specify the state of each particle at time t by its location on this lattice. (A more realistic model of diffusion in the plasma membrane as illustrated in Figure 1 would consider the hopping of particles between nearest-neighbor, well-mixed compartments arranged on a two-dimensional lattice; in this paper we focus on the simpler one-dimensional case.) The resulting process has two levels of stochasticity: one due to the jump process describing the hopping of individual particles between

neighboring sites on the lattice, and one due to the random switching of the gate; see Figure 2 (B). While this process has been mentioned in previous papers on the topic of protein diffusion in cell membranes, the complexity of the master equation resulting from such a process has prohibited analytical investigation. Therefore, the problem of determining the existence and location of one or more dynamic gates in a spatially extended domain has not been studied in detail.

In this paper we develop a mathematical framework for studying the above type of problem in the mean-field or thermodynamic limit $C_{\rm tot} \to \infty$, where $C_{\rm tot}$ is the number of identical, independent random walkers moving in the same switching environment. Suppose that the state of the environment at time t is denoted by $s(t) \in \{0, 1\}$. Each realization of the environment up to time t, $\sigma(t) = \{s(\tau), 0 \le \tau < t\}$ will typically generate a different particle distribution $P(n, t)$—in the mean-field limit this represents the fraction of particles at lattice site state n at time t, given some initial distribution $P_0(n)$. The presence of the random environment means that the particle distribution $P(n, t)$ is itself a random variable; that is, it implicitly depends on σ. One finds that P evolves according to a so-called stochastic hybrid system (SHS) [11]. Introducing the rth order moments

$$C^{(r)}(n_1, \dots, n_r, s) = \mathbb{E}_\sigma[P(n_1, t) \dots P(n_r, t) 1_{s(t)=s}],$$

where expectation is taken with respect to realizations σ conditioned on the environmental state at time t being s, $s(t) = s$, one can derive a closed hierarchy of moment equations in the form of deterministic master equations. This then establishes a relationship between $C^{(r)}(n_1, \dots, n_r, s)$ and the joint probability distribution for r random walkers having positions $n_1, \dots, n_r$ at time t, given that the random environment is currently in state $s(t) = s$ (but previous states of the environment are not fixed). Consider, in particular, the first moment

$$\pi_{n,s}(t) = \mathbb{E}_\sigma[P(n, t) 1_{s(t)=s}].$$

We find that $\pi_{n,s}(t)$ satisfies the same deterministic master equation as $p(n, s, t)$, which is the probability that a single random walker is at site n at time t, given that the environment is currently in state s. The difference between the two distributions $P(n, t)$ and $p(n, s, t)$ is illustrated in Figure 2 (C). Note that in the absence of a stochastic gate, the two distributions are equivalent, since both sample the same underlying BDP. This raises the issue of how the statistics obtained from the two perspectives differ in the presence of a stochastic gate. An analogous issue has recently been explored within the context of partial differential equations (PDEs) in switching environments [6, 4, 5]. These studies analyze the drift-diffusion equation in a domain with switching boundaries, in which the rth moments of the stochastic PDE determine the statistics of r particles moving in the same random environment.

In developing our analysis we will make repeated use of the following acronyms:

- DSBDP (doubly stochastic birth-death process): A BDP that has stochastic transition rates due to a randomly switching environment. In the random walk model this is due to stochastic gating.
- QBDP (quasi birth-death process): Formulation of a DSBDP as a bivariate Markov process, in which one simultaneously samples over multiple realizations of the BDP and the switching environment. It determines the state probability of a single random walker.
- SHS (stochastic hybrid system): Formulation of a DSBDP in which one samples over multiple realizations of the BDP for a single realization of the

randomly switching environment. It describes the piecewise deterministic evolution equation for the probability distribution of a large population of random walkers evolving in the same environment, which is a random variable depending on realizations of the random environment.

The structure of the paper is as follows. We begin by considering the two distinct formulations of a DSBDP given by a QBDP and an SHS, respectively (section 2). We analyze the relationship between the two formulations in section 3. Exploiting the fact that the piecewise deterministic dynamics of the SHS is linear in the probability distribution, we derive a hierarchy of moment equations that provide statistical information regarding the site occupancies (section 3). We also establish a probabilistic relationship between the moments obtained from the SHS framework, and the statistics of a finite number of particles in the QBDP framework. That is, we show that the r-point correlations are related to the joint probability densities of r noninteracting particles in the same switching environment. We then apply our theoretical results to the particular example of a population of particles walking on a one-dimensional lattice with a dynamic gate at some unknown location (section 4). Solving the moment equations for the SHS, we extract statistical information about the location and dynamics of the gate in terms of how the mean and variance of site occupancies vary with distance of a given site from the gate.

Finally, note that there is a considerable amount of literature on so-called doubly stochastic Poisson processes (DSPPs), also known as Cox processes, but, as far as we are aware, there has been very little work on DSBDPs. DSPPs were first introduced by Cox [9] as a generalization of an inhomogeneous Poisson process, in which the time-dependent transition rate depends on a second, independent stochastic process. The general theory of DSPPs was subsequently developed by Grandell [14]. Example applications include photon and electron detection [26], occurrences of credit events in finance [24], and neural coding [28, 20].

2. Model formulation. A BDP is an example of a Markov process with a discrete state space (which could be infinite) $\mathcal{N} = \{0, 1, \ldots, L\} \subset \mathbb{N}$. Let the random variable $N(t) \in \mathcal{N}$ denote the current state of this stochastic process. We will let α_n and β_n denote the transition rates from state n to $n+1$ and n to $n-1$, respectively. Consider the probability distribution for $N(t)$, which we denote by $p(n,t)$. The invariant density, or steady-state distribution, denoted $p^*(n)$, is defined by $p^*(n) = \lim_{t\to\infty} p(n,t)$ if it exists. Provided $\alpha_n \neq 0$ and $\beta_{n+1} \neq 0$ for all $0 \leq n < L$, the BDP is ergodic and the existence of $p^*(n)$ is guaranteed. Following a derivation which can be found in [15], we obtain the birth-death master equation

$$\frac{d}{dt}p(n,t) = \alpha_{n-1}p(n-1,t) + \beta_{n+1}p(n+1,t) - [\alpha_n + \beta_n]p(n,t) \tag{2.1}$$

with $\alpha_{-1} = \beta_0 = 0$ and $\alpha_L = \beta_{L+1} = 0$. It is convenient to introduce the vector $\boldsymbol{p}(t) = [p(0,t), \ldots, p(L,t)]^T$ and an appropriate matrix A so that we can write this equation in matrix form: $d\boldsymbol{p}/dt = A\boldsymbol{p}$. The adjoint matrix A^T is known as the generator of the Markov process. The steady-state distribution $\boldsymbol{p}^* = [p^*(1), \ldots, p^*(L)]^T$ satisfies $A\boldsymbol{p}^* = 0$ and $\mathbf{1}^T\boldsymbol{p}^* = 1$ and it is well known that this definition of $\boldsymbol{p}^*$ is equivalent to the limit definition given above [15].

2.1. Doubly stochastic BDP. Motivated by the aforementioned biological example of membrane diffusion, we introduce an added level of stochasticity to the BDP by allowing the transition rates α_n, β_n to depend on a second, independent discrete stochastic variable $S(t)$. The latter takes values in a discrete state space

$\mathcal{S} = \{0, \ldots, M-1\} \subset \mathbb{N}$, and transitions between states in $\mathcal{S}$ occur according to a jump process with rates $\omega_{ss'}$. For simplicity, we assume that the transition rates are independent of $N(t)$. If $q(s,t)$ is the probability distribution for the process $S(t)$, the vector $\boldsymbol{q} = [q(0,t), \ldots, q(M-1,t)]^T$ is governed by the master equation

$$\frac{d}{dt}\boldsymbol{q} = \Omega \boldsymbol{q}, \tag{2.2}$$

where the matrix Ω has entries

$$\Omega_{ss'} = \omega_{ss'} - \delta_{s,s'} \sum_{k \in \mathcal{S}} \omega_{ks'}.$$

We will assume that the matrix of transition rates $\omega_{ss'}$ is irreducible, so that there exists a unique steady-state distribution $\boldsymbol{q}^*$ satisfying $\Omega \boldsymbol{q}^* = 0$ and $\mathbf{1}^T \boldsymbol{q}^* = 1$. Note that $S(t)$ need not evolve according to a BDP, so the transition rates have a more general structure on the state space $\mathcal{S}$. We will refer to $S(t)$ as an *environmental* variable, while $N(t)$ will be referred to as a *state* variable. This terminology will also be applied to associated objects such as transition rates. For example, we refer to α_n, β_n as state transition (or birth-death) rates, while $\omega_{ss'}$ is an environmental transition rate.

DEFINITION 2.1. *A* DSBDP *is an inhomogeneous BDP with stochastic birth-death rates $\alpha_n(S(t))$ and $\beta_n(S(t))$, and environmental transition rates $\omega_{ss'}$.*

2.2. Two alternative probabilistic formulations of a DSBDP. We now consider two complementary probabilistic formulations of a DSBDP.

2.2.1. DSBDP as a level-dependent QBDP. The DSBDP is an example of a bivariate Markov process for the random variable

$$Z(t) = (N(t), S(t)) \in \mathcal{N} \times \mathcal{S}.$$

Let $p(n,s,t)$ be the joint probability distribution of $N(t)$ and $S(t)$ given the initial conditions $N(0) = n_0$ and $S(0) = s_0$; that is,

$$p(n,s,t) = \mathbb{P}[N(t) = n, S(t) = s | N(0) = n_0, S(0) = s_0]. \tag{2.3}$$

We will interpret $p(n,s,t)$ as the probability that a single particle is in state n at time t, given that the environment is in state s. The master equation for $p(n,s,t)$ takes the form

$$\begin{aligned} \frac{d}{dt}p(n,s,t) &= \alpha_{n-1,s}p(n-1,s,t) + \beta_{n+1,s}p(n+1,s,t) - [\alpha_{n,s} + \beta_{n,s}]p(n,s,t) \\ &\quad + \sum_{s'=0}^{M-1} [\omega_{ss'}p(n,s',t) - \omega_{s's}p(n,s,t)], \end{aligned} \tag{2.4}$$

where $\alpha_{n,s} = \alpha_n(s)$ and $\beta_{n,s} = \beta_n(s)$. Equation (2.4) is supplemented by the initial condition $p(n,s,0) = \delta_{n,n_0}\delta_{s,s_0}$.

The right-hand side of the master equation (2.4) has an obvious intuitive interpretation: the first line represents the flow of probability due to the state transitions, while the second line represents the flow due to environmental transitions. Equation (2.4) is an example of a level-dependent QBDP. More generally, a QBDP is a Markov

process on some subset of $\mathbb{N} \times \mathbb{N}$ where the transitions in the first variable (the state) are restricted to nearest neighbors, but the transitions in the second variable (the environment) may be arbitrary. If the state transitions depend on the environmental label, then this becomes a level-dependent QBDP. Such processes have applications in queuing theory and communications systems, but little is known about them in general [19]. To our knowledge, the connection between a general level-dependent QBDP and a DSBDP has not previously been made.

In many applications we are not particularly interested in the environmental variable, but rather the total probability that a particle is in discrete state n. This is due to the fact that in many biological systems the random variable $N(t)$ can be observed, whereas $S(t)$ is hidden. We thus introduce the unconditional probability distribution

$$\overline{p}(n,t) = \sum_{s=1}^{M} p(n,s,t). \tag{2.5}$$

The corresponding steady-state distribution is then given by

$$\overline{p}^*(n) = \sum_{s=1}^{M} p^*(n,s), \quad \overline{p}^*(n,s) = \lim_{t\to\infty} p(n,s,t).$$

We will assume throughout that the transition matrix of the Markov process $Z(t)$ is irreducible.

2.2.2. DSBDP as an SHS. For a given realization of the stochastic process $S(t)$, $\sigma(t) = \{s(\tau), 0 \le \tau < t\}$, the conditional probability distribution

$$P(n,t) = \mathbb{P}[N(t) = n | \{s(\tau), 0 \le \tau < t\}] \tag{2.6}$$

evolves according to the inhomogeneous birth-death master equation

$$\frac{d}{dt}P(n,t) = \alpha_{n-1}(s(t))P(n-1,t) + \beta_{n+1}(s(t))P(n+1,t) - [\alpha_n(s(t)) + \beta_n(s(t))]P(n,t). \tag{2.7}$$

The initial conditions are taken to be $P(n,0) = P_0(n)$ and $S(0) = s_0$. We will interpret $P(n,t)$ as the probability distribution for an infinite population of independent, identical particles subject to a single realization of the random environment.[1] Observing multiple independent particles evolving in the same random environment allows us to separate out the sampling of the BDP $N(t)$ and the stochastic process $S(t)$. It follows that multiple realizations of $S(t)$ will produce a "distribution of distributions." In order to analyze the latter, we replace $s(t)$ in (2.7) by the random environmental variable $S(t)$. Setting $\boldsymbol{P}(t) = [P(0,t), \ldots, P(L,t)]^T$, we can rewrite (2.7) in the

[1] This interpretation relies on the strong law of large numbers. That is, consider C_{tot} particles undergoing a DSBDP in the same switching environment and let $C(n,t)/C_{\text{tot}}$ be the fraction of particles at site n at time t. The strong law of large numbers implies $C(n_1,t)\ldots C(n_r,t)C_{\text{tot}}^{-r} \to P(n_1,t)\ldots P(n_r,t)$ a.s. Taking the expectation of both sides of this expression with respect to the realizations of $S(t)$ and applying the dominated convergence theorem yields $\lim_{C_{\text{tot}}\to\infty} C_{\text{tot}}^{-r}\mathbb{E}_\sigma[C_{n_1}(t)\ldots C_{n_r}(t)] = \mathbb{E}_\sigma\left[P(n_1,t)\ldots P(n_r,t)\mathbf{1}_{S(t)=s}\right]$. One should also note that it is straightforward to apply recent technical work on error bounds for stochastic hybrid approximations of chemical reaction networks to obtain error bounds on the approximation of $P(n,t)$ by $C(n,t)/C_{\text{tot}}$ for large but finite C_{tot}. see for example [10, 17] We have omitted these technical results since our goal is not to obtain error bounds for modeling purposes, but rather to explore the various conceptual interpretations of the SHS formation.

matrix form

$$\frac{d}{dt}\boldsymbol{P} = A_s\boldsymbol{P}, \tag{2.8}$$

where A_s is the generator of the BDP for $S(t) = s \in \mathcal{S}$. That is,

$$\sum_{k=0}^{L}[A_s]_{kn}P(k,t) = \alpha_{n-1,s}P(n-1,t) + \beta_{n+1,s}P(n+1,t) - [\alpha_{n,s} + \beta_{n,s}]P(n,t). \tag{2.9}$$

Equation (2.8) holds between jumps in the environmental variable $S(t)$, which occur according to the master equation (2.2). Equations (2.8) and (2.2) are an example of an SHS, also known as a piecewise deterministic Markov process [11]. Let $\varrho(s,\boldsymbol{p},t)$ denote the joint probability density of $\boldsymbol{P}$ and S, that is,

$$\varrho(s,\boldsymbol{p},t)d\boldsymbol{p} = \mathbb{P}[S(t) = s, \boldsymbol{P}(t) \in (\boldsymbol{p},\boldsymbol{p}+d\boldsymbol{p})|s(0) = s_0, \boldsymbol{P}(0) = \boldsymbol{p}_0].$$

The vector $\boldsymbol{\varrho}(\boldsymbol{p},t) = [\varrho(1,\boldsymbol{p},t),\dots,\varrho(M,\boldsymbol{p},t)]^T$ evolves according to the differential Chapman–Kolmogorov (dCK) equation

$$\frac{\partial}{\partial t}\varrho(s,\boldsymbol{p},t) = -\nabla_{\boldsymbol{p}}\cdot[(A_s\boldsymbol{p})\varrho(s,\boldsymbol{p},t)] + \sum_{s'=0}^{M-1}\Omega_{ss'}\varrho(s',\boldsymbol{p},t). \tag{2.10}$$

Noting that $\boldsymbol{p}$ is a probability density on $\mathbb{R}^{L+1}$, the spatial domain of (2.10) must be the L-simplex

$$\Delta^L = \left\{\boldsymbol{p} \in \mathbb{R}^{L+1} | \mathbf{1}^T\boldsymbol{p} = 1,\, p(i) \geq 0 \text{ for all } i = 0,\dots,L\right\}.$$

Finally, we impose reflecting boundary conditions so that $\varrho(s,\boldsymbol{p},t) = 0$ for $\boldsymbol{p} \in \partial\Delta^L$ and initial conditions

$$\varrho(s,\boldsymbol{p},0) = \delta_{s,s_0}\delta(\boldsymbol{p}-\boldsymbol{p}_0).$$

3. Moments of the SHS. In the previous section we introduced two mathematically different descriptions of a DSBDP. The relationship between the two formulations can be expressed by the following theorem.

THEOREM 3.1. *The relationship between the QBDP and SHS formulations of a DSBDP is given by*

$$p(n,s,t) = \pi_{n,s}(t), \tag{3.1}$$

where

$$\pi_n(s,t) \equiv \mathbb{E}_\sigma\left[P(n,t)\mathbf{1}_{S(t)=s}\right] = \int_{\Delta^L} p(n)\varrho(s,\boldsymbol{p},t)d\boldsymbol{p}. \tag{3.2}$$

That is, the probability distribution of the QBDP corresponds to a first moment of the SHS. It follows that

$$p^*(n,s) \equiv \lim_{t\to\infty} p(n,s,t) = \lim_{t\to\infty}\int_{\Delta^L} p(n)\varrho(s,\boldsymbol{p},t)d\boldsymbol{p} = \int_{\Delta^L} p(n)\varrho^*(s,\boldsymbol{p})d\boldsymbol{p},$$

assuming that the dCK equation (2.10) *has a stationary solution* $\varrho^*(s,\boldsymbol{p})$.

Proof. First note that (3.2) immediately follows from the definition of $\varrho(s, \boldsymbol{p}, t)$. In order to establish (3.1), differentiate (3.2) with respect to time, substitute for $\partial\varrho/\partial t$ using (2.10) and integrate by parts. This yields the master equation

$$\begin{aligned}\frac{d}{dt}\pi_{n,s}(t) &= \sum_{k=0}^{L}[A_s]_{kn}\pi_{k,s}(t) + \sum_{s'=0}^{M-1}\Omega_{ss'}\pi_{n,s'}(t)\\ &= \alpha_{n-1,s}\pi_{n-1,s}(t) + \beta_{n+1,s}\pi_{n+1,s}(t)\\ &\quad - [\alpha_{n,s}+\beta_{n,s}]\pi_{n,s}(t) + \sum_{s'=0}^{M-1}[\omega_{ss'}\pi_{n,s'}(t) - \omega_{s's}\pi_{n,s}(t)].\end{aligned} \tag{3.3}$$

We then note the equivalence of (3.3) and (2.4). ∎

The obvious question to ask is how to generalize (3.1) to relate the rth moments of $P(n,t)$,

$$\pi^{(r)}_{n_1\dots n_r,s}(t) \equiv \mathbb{E}_\sigma\left[P(n_1,t)\dots P(n_r,t)\mathbf{1}_{S(t)=s}\right] = \int_{\Delta^L} p(n_1)\dots p(n_r)\varrho_s(\boldsymbol{p},t)d\boldsymbol{p}, \tag{3.4}$$

to the statistics of a finite number of particles undergoing the QBDP. Generalizing the calculation of the first moments, we obtain the more general *moment flow equations*

$$\begin{aligned}\frac{d}{dt}\pi^{(r)}_{n_1\dots n_r,s}(t) &= \sum_{i=1}^{r}\sum_{k=0}^{L}[A_s]_{kn_i}\int_{\Delta^L} p(k)\prod_{j=1,j\neq i}^{r}p(n_j)d\boldsymbol{p} + \sum_{s'=0}^{M-1}\Omega_{ss'}\pi^{(r)}_{n_1\dots n_r,s'}\\ &= \sum_{i=1}^{r}\sum_{k=0}^{L}[A_s]_{kn_i}\pi^{(r)}_{kn_1\dots n_{i-1}n_{i+1}\dots n_r,s}(t) + \sum_{s'=0}^{M-1}\Omega_{ss'}\pi^{(r)}_{n_1\dots n_r,s'}(t).\end{aligned} \tag{3.5}$$

Now consider the joint probability distribution for r particles undergoing a QBDP in the same environment, with $N_j(t)$ the state of the jth particle at time t, $j = 1,\dots,r$, and $S(t) = s$:

$$\begin{aligned}f(n_1,\dots,n_r,s,t) &= \mathbb{P}[N_1(t)=n_1,\dots,N_r(t)=n_r,S(t)=s|N_1(0)\\ &\quad = n_{1,0},\dots,N_r(0)=n_{r,0},S(0)=s_0].\end{aligned}$$

Here it makes sense to consider the joint probability distribution for the particle states $N_j(t)$ and the environmental state $S(t)$, because we are considering all these particles to be in the same environment. From a modeling perspective this means that whatever mechanism changes the rates is not associated with the particles, but the environment they are evolving in. Writing out the master equation for the evolution of $f(n_1,\dots,n_r,s)$, we find that it is exactly the form of (3.5). This yields the following result which generalizes Theorem 3.1.

THEOREM 3.2. *The joint probability of r independent particles undergoing a QBDP in the same random environment with initial states $N_j(t) = n_{j,0}$ and $S(t) = s_0$ is related to the rth moments $\pi^{(r)}$ according to*

$$f(n_1,\dots,n_r,s,t) = \pi^{(r)}_{n_1\dots n_r,s}(t)$$

with the initial conditions

$$\pi^{(r)}_{n_1\dots n_r,s}(0) = \delta_{n_1,n_{1,0}}\dots\delta_{n_r,n_{r,0}}\delta_{s,s_0}.$$

4. Application of SHS formulation to spatially extended gating model. Having provided a mathematical formulation of a DSBDP, we now return to the example considered in the introduction. Namely, we are interested in modeling the spatial dynamics of diffusing proteins in a plasma membrane with dynamically gated corrals. We begin by reviewing the spatially homogeneous stochastic gating model of Brown and collaborators [8], in which diffusion within a bounded domain is relatively fast, so that the molecules are well mixed and one can ignore spatial effects within the domain—such a domain corresponds to a single lattice site in our spatially extended model. Brown and collaborators study this problem analytically by explicitly studying the BDP for the number of particles inside a single confinement domain. (The exterior of the domain is simply treated as a homogeneous region with a constant background concentration of particles—particle conservation is not imposed.) Their method allows one to obtain exact results for the mean and variance of the number of particles within the domain when the effects of the larger spatial structure can be ignored. In contrast, the stochastic hybrid formulation developed in the previous section allows one to obtain approximate statistics for a large number of proteins in a plasma membrane with multiple homogeneous confinement domains linked by gates. The basic idea is illustrated in Figures 2 (A) and (B).

4.1. Stochastic gating model of confinement. Let $P_l(t)$ be the probability that there are l free particles within a single domain at time t; see Figure 3. (In order to avoid confusion, we use l to denote the number of particles in a single compartment and n to index a compartment on a spatially extended lattice.) Denote the state of the stochastic gate at time t to be the binary random variable $s(t)$ with $s(t) = 1$ ($s(t) = 0$) corresponding to the open (closed) state. The opening and closing of the stochastic gate is governed by the two-state Markov process with a density evolving according to (2.2) with $q(0,t) = \mathbb{P}[s(t) = 0]$, $q(1,t) = \mathbb{P}[s(t) = 1]$, and

$$\Omega = \begin{bmatrix} -a & b \\ a & -b \end{bmatrix}. \tag{4.1}$$

Particles can only transfer between the exterior and interior of the domain when the gate is open, in which case the rates of outflux and influx are α and β. It is assumed that a constant background concentration c_0 of particles exists in the exterior, so β is proportional to c_0. The probability distribution $P_l(t)$ evolves according to the time-inhomogeneous birth-death master equation

$$\frac{dP_l}{dt} = s(t)\left[\beta P_{l-1}(t) + (l+1)\alpha P_{l+1}(t) - (\beta + \alpha l)P_l(t)\right] \tag{4.2}$$

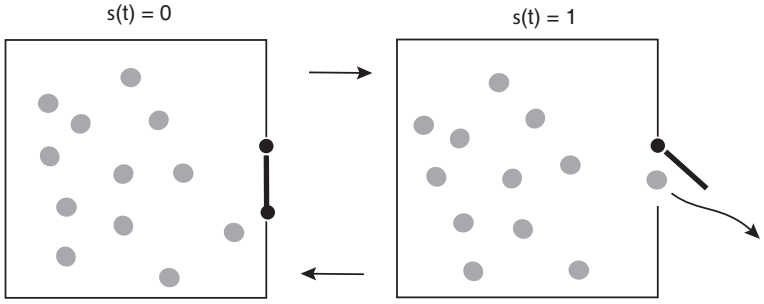

FIG. 3. *Escape from a domain with a single stochastic gate.*

with $l \geq 0$ and $P_{-1}(t) \equiv 0$. The positive terms on the right-hand side represent the various transitions into the state (l), whereas the negative terms represent the various transitions from the state (l). The initial condition is $P_l(0) = \delta_{l,l_0}$; i.e., at time $t = 0$ there are l_0 free particles within the domain. First, suppose that the gate is always open so that (4.2) reduces to the autonomous master equation

$$\frac{dP_l}{dt} = \beta P_{l-1}(t) + (l+1)\alpha P_{l+1}(t) - (\beta + \alpha l)P_l(t). \tag{4.3}$$

The mean concentration of particles in the domain, $x(t) = \mathbb{E}[l(t)]/V$, where V is the volume of the domain, evolves according to the simple kinetic equation

$$\frac{dx}{dt} = \beta/V - \alpha x.$$

This has a steady-state solution $l = Vx = \beta/\alpha$.

Equation (4.3) is a rare example of a master equation that can be solved exactly, and one finds that $P_l(t)$ is given by a Poisson distribution. The simplest way to see this is to introduce the generating function

$$G(z,t) = \sum_{k \geq 0} z^k P_k(t)$$

and substitute into (4.3):

$$\frac{\partial G}{\partial t} + \alpha(z-1)\frac{\partial G}{\partial z} = \beta(z-1)G.$$

This is a linear first-order PDE with nonconstant coefficients. A standard method for solving such equations is the *method of characteristics*. Given the initial condition $P_l(0) = \delta_{l,l_0}$, we have $G(z,0) = z^{l_0}$ and

$$G(z,t) = [1 + \mathrm{e}^{-\alpha t}(z-1)]^{l_0} \mathrm{e}^{\beta\left(1-\mathrm{e}^{-\alpha t}\right)(z-1)/\alpha}. \tag{4.4}$$

We now Taylor expand $G(z,t)$ in powers of z and thus find that for $l_0 = 0$ (bounded domain is initially empty),

$$P_l(t) = \mathrm{e}^{-\lambda(t)}\frac{\lambda(t)^l}{l!}, \quad \lambda(t) = \frac{\beta}{\alpha}(1 - \mathrm{e}^{-\alpha t}), \tag{4.5}$$

which is a time-dependent Poisson distribution of rate $\lambda(t)$. It immediately follows that

$$\mathbb{E}[l(t)] = \lambda(t), \quad \mathrm{Var}[l(t)] = \lambda(t).$$

In the more general case $l_0 \neq 0$, the mean and variance can be calculated from the formulae

$$\mathbb{E}[l(t)] = \left.\frac{\partial G(z,t)}{\partial z}\right|_{z=1}, \quad \mathbb{E}[(l^2(t) - l(t))] = \left.\frac{\partial^2 G(z,t)}{\partial z^2}\right|_{z=1}.$$

Calculating these derivatives yields

$$\mathbb{E}[l(t)] = (l_0 - \beta/\alpha)\mathrm{e}^{-\alpha t} + \beta/\alpha, \; \mathrm{Var}[l(t)] = \mathbb{E}[l(t)] - l_0\mathrm{e}^{-2\alpha t}.$$

4.2. Kubo equation. Let us now turn to the full stochastic gating model (4.2), in which the state of the gate is given by the stochastic variable $s(t)$ so that there are two levels of stochasticity: the stochastic process of exchange of particles when the gate is open, and the random opening and closing of the gate itself. For a given realization $\sigma(t) = \{s(\tau), 0 \leq \tau < t\}$ of the stochastic gate, we can repeat the analysis of the autonomous master equation (4.3), except that

$$\mathrm{e}^{-\alpha t} \to X(t) \equiv \mathrm{e}^{-\alpha \int_0^t s(t')dt'} \tag{4.6}$$

in the definition of $\lambda(t)$; see (4.5). It follows that different realizations of $s(t)$ will yield different values of the mean and variance. Hence, a more useful characterization of the statistics is obtained by averaging $X(t)$ with respect to all possible stochastic realizations of the gate, which is denoted by $\mathbb{E}_\sigma[X]$. The latter can be performed using a method originally developed by Kubo [21] in the study of spectral line broadening in a quantum system, and subsequently extended to chemical rate processes with dynamical disorder by Zwanzig [34].

Following Kubo [21], we differentiate (4.6) with respect to time to obtain the piecewise deterministic equation

$$\frac{dX}{dt} = -\alpha s(t) X(t), \tag{4.7}$$

where $s(t)$ is a discrete random variable that switches between $s = 1$ and $s = 0$ according to (2.2). Introduce the probability densities $p_k(x,t)$ with $p_k(x,t)dx = \mathrm{Prob}[s(t) = k,\, x \leq X(t) \leq x + dx]$, $k = 0, 1$, and initial conditions

$$p_k(x,0) = \delta(x-1)q_k^*.$$

Here q_k^*, $k = 0, 1$, are the stationary probability distributions of the two-state Markov process with transition matrix (4.1):

$$q_0^* = \frac{b}{a+b}, \quad q_1^* = \frac{a}{a+b}.$$

These densities evolve according to the dCK equation

$$\frac{\partial p_0}{\partial t} = bp_1 - ap_0, \tag{4.8a}$$

$$\frac{\partial p_1}{\partial t} = \alpha \frac{\partial (x p_1)}{\partial x} - bp_1 + ap_0. \tag{4.8b}$$

This takes into account the piecewise deterministic decay of x when the gate is open, given by the Liouville term in (4.8b), and transitions between the two states of the gate. We now make the observation that $p(x,t) = p_0(x,t) + p_1(x,t)$ is the probability density for the stochastic process $X(t)$, which has the formal solution (4.6) together with the constraint that the initial state of the gate $s(0)$ is a random variable distributed according to the stationary distribution $\boldsymbol{q}^*$. Thus, finding the mean of $X(t)$ with respect to the stochastic process $\mu(t)$ is equivalent to finding the conditional means

$$\mu_k(t) = \int_0^\infty x p_k(x,t)dx, \quad k = 0, 1,$$

and setting

$$\mathbb{E}_\sigma[X(t)] = \mu_0(t) + \mu_1(t).$$

In order to determine $\mu_k(t)$, take the first moments of (4.8a) and (4.8b). This yields the matrix equation

$$\frac{d}{dt}\begin{bmatrix} \mu_0(t) \\ \mu_1(t) \end{bmatrix} = -\mathcal{A}\begin{bmatrix} \mu_0(t) \\ \mu_1(t) \end{bmatrix}, \quad \mathcal{A} = \begin{bmatrix} -a & b+\alpha \\ a & -b \end{bmatrix}, \tag{4.9}$$

which has the solution

$$\begin{bmatrix} \mu_0(t) \\ \mu_1(t) \end{bmatrix} = \mathrm{e}^{-t\mathcal{A}}\boldsymbol{q}^*.$$

A similar analysis can be carried out for second moments. One thus finds that the σ-averaged mean and variance of $l(t)$ are

$$\mathbb{E}_\sigma[l] = (l_0 - \beta/\alpha)\mathbb{E}_\sigma[X] + \beta/\alpha, \tag{4.10}$$

$$\mathrm{var}_\sigma[l] = \mathbb{E}_\sigma[l] - l_0\mathbb{E}_\sigma[X^2] + (l_0 - \beta/\alpha)^2\left(\mathbb{E}_\sigma[X] - \mathbb{E}_\sigma[X]^2\right), \tag{4.11}$$

where

$$\mathbb{E}_\sigma\left[X(t)^r\right] = \mathbf{1}^T \exp\left(-t\begin{bmatrix} -a & b+r\alpha \\ a & -b \end{bmatrix}\right)\boldsymbol{q}^* \tag{4.12}$$

for $r = 1, 2$. The averages $\mathbb{E}_\sigma[X^r]$, $r = 1, 2$, approach zero as time increases, hence the steady-state mean and variance are both equal to β/α.

4.3. SHS formulation of spatially extended gating model. As we mentioned earlier, the model developed by Brown and collaborators includes the effects of an extended spatial domain implicitly by not conserving the total number of particles in the system. This is a significant simplification of the underlying biophysical process, namely, the diffusion of a large population of proteins within the cell membrane, which consists of multiple confinement domains; see Figure 1. Using the above methods, this problem becomes highly intractable for more than two connected confinement domains, even for one dynamic gate. On the other hand, if we consider an infinite population of particles, the model without dynamic gating becomes deterministic, and the statistics of the density of particles on a given lattice site in the presence of a dynamic gate can be obtained from the SHS formulation.

Returning to the spatially extended model of protein diffusion in a plasma membrane, for a large number of particles we can study the effects of a spatially extended lattice to the right of the dynamic gate. Specifically, we consider a DSBDP (Definition 2.1) with two environmental states ($M = 2$), Ω given by (4.1), and

$$\alpha_{n,1} = \alpha, \quad \beta_{n,1} = \beta, \quad \alpha_{n,0} = (1 - \delta_{n,0})\alpha, \quad \beta_{n,0} = (1 - \delta_{n,1})\beta.$$

We assume that all particles are initially at the leftmost site $n = 0$ (corresponding to the confinement domain of Brown et al. [8]) and that there is a dynamical gate between the sites $n = 0$ and $n = 1$. Hence, when the gate is closed ($s(t) = 0$), no particles can transfer between the first two lattice sites, that is, $\alpha_{0,0} = \beta_{1,0} = 0$. Figure 4 illustrates the difference between the normalized first moments determined using, respectively, the nonconservation model of Brown et al. for a single confinement domain and the SHS formulation of the DSBDP for multiple confinement domains on a lattice. The former is given by $\mathbb{E}[l(t)]/l_0$, where l_0 is the initial number of particles in the single confinement domain and $\mathbb{E}[l(t)]$ satisfies (4.10); the latter is given by $\pi_0(t)$, where

$$\pi_n(t) = \mathbb{E}_\sigma[P(n,t)] = \sum_{s=0,1} \pi_{n,s}(t) = \overline{p}(n,t);$$

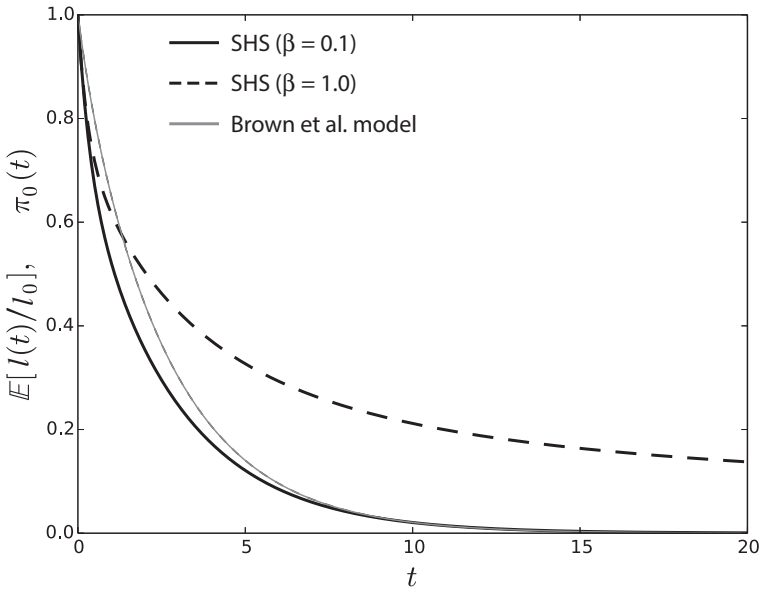

FIG. 4. *A comparison of first-order statistics obtained by Brown et al.* [8] *(gray curve) using* (4.10) *with the results obtained from the SHS formulation (black curves) using* (2.4)*, in which the system is spatially extended to the right of the dynamic gate by including* $L = 100$ *ungated regions. The dashed black curve corresponds to* $\beta = 1$*, while the solid black curve corresponds to* $\beta = 0.1$*. The value of* β *has little effect on the first moment of the Brown et al.* [8] *model, so we only see one gray curve. Other parameter values used are* $l_0 = 100$ *and gating rates* $a = b = 1$*.*

see (2.5) and Theorem 3.1. Note that in the limit $\beta \to 0$, both formulations yield the same result, since the spatial extent of the domain surrounding the leftmost site becomes unimportant.

The most realistic generalization of Brown's et al. model would include an independent, stochastic gate at each lattice site in a two-dimensional domain. The SHS formulation could certainly be applied to this, but we simplify matters here and consider the problem of understanding how the effect of a single dynamical gate depends on the distance of a given site n from the gate. Figure 4 shows the results for $n = 0$. We further generalize the model of Brown et al. by also considering a partial or rectifying gate, which switches between states allowing particles to pass from the left ($s = 0$) and from the right ($s = 1$), respectively. In this case Ω is still given by (4.1) and

$$\alpha_{n,0} = \alpha, \quad \beta_{n,1} = \beta, \quad \alpha_{n,1} = (1 - \delta_{n,0})\alpha, \quad \beta_{n,0} = (1 - \delta_{n,1})\beta.$$

We can in principle approximate the probability distribution for the number of particles at any lattice site. It is of course more reasonable to simply look at the mean and variance. If we can observe the time-dependent distributions, we can easily compare them to numerical simulations of the linear systems for $\pi^{(r)}$. In Figure 5 we show the time evolution of the first moment $\pi_n(t)$ and variance $\mathrm{Var}_n(t)$ at three different lattice sites and for different gating rates. Here

$$\mathrm{Var}_n(t) = \mathbb{E}_\sigma[P(n,t)P(n,t)] - (\mathbb{E}_\sigma[P(n,t)])^2 = \sum_{s=0,1} \pi^{(2)}_{nn,s}(t) - \pi_n(t)^2;$$

see (3.4). This figure demonstrates how the SHS formulation can be used to study the general problem of determining the existence, location, and properties of a dynamic

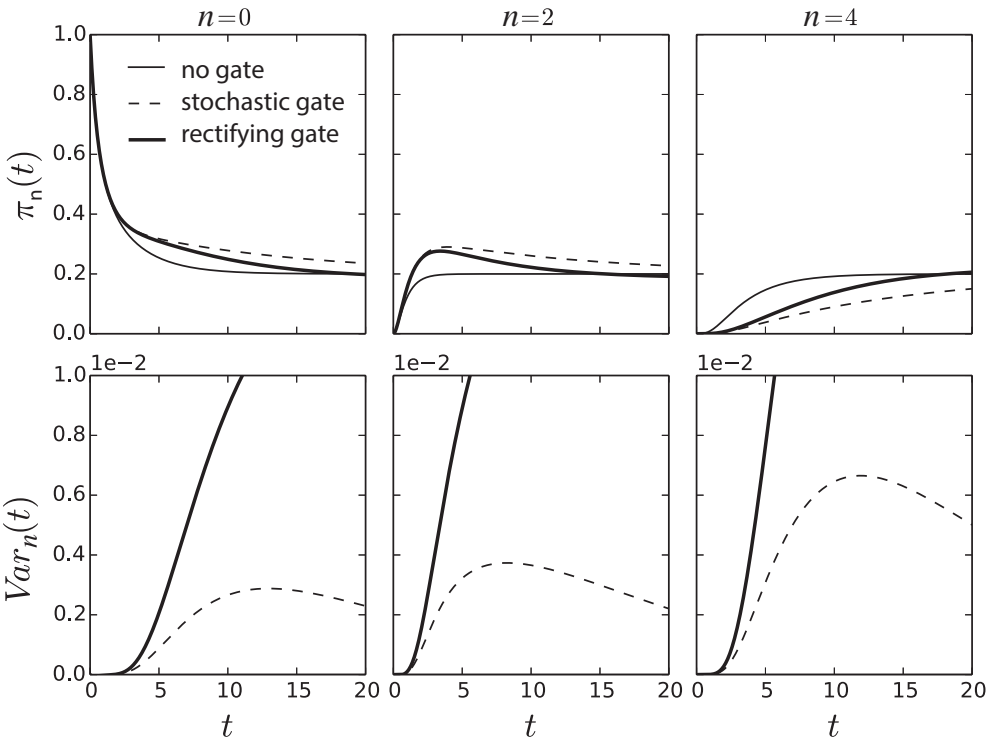

FIG. 5. *Time-dependent mean and variance of $P(n,t)$ for the SHS formulation at three different lattice sites computed using the SHS formulation. The initial conditions are $\pi_n(0) = \delta_{0,n}$ and parameters are $a = 0.1, b = 0.1, \alpha = 1, \beta = 1$. Note that in the absence of a gate there are no fluctuations (zero variance) so only two curves are shown in the bottom row of figures.*

gate based on time series data of particles evolving in a switching environment. We can see that, analogous to the well known over-dispersion for doubly stochastic Poisson processes [9], observations closer to the gate produce a greater variance which can be used to identify its location. The mean trajectories also appear to change qualitatively as we approach the gate. In particular for $n = 2$ the mean is no longer monotonically increasing for the gated trajectories. In terms of distinguishing between the two types of gating, the variance is clearly more effective because the partial gate produces qualitatively similar trajectories for the mean, but qualitatively different trajectories in the variance.

5. Discussion. To summarize, we analyzed a population of randomly walking particles in a stochastically switching environment by formulating the model as a stochastic hybrid system. The latter describes the evolution of the probability distribution of the particles in the mean-field limit and for a particular realization of the switching environment. The probability distribution is a random variable with respect to different realizations. We derived a hierarchy of moment equations for the probability distribution averaged over these realizations, which took the form of deterministic master equations. As a specific example, we considered a population of particles walking on a one-dimensional lattice with a dynamic gate at some unknown location. Solving the moment equations for the stochastic hybrid system allowed us

to determine how the mean and variance of the distribution varied with distance from the gate. This has potential applications in the analysis of time series data obtained from biophysical experiments on the diffusion of particles in the plasma membrane of cells. In addition, we established a relationship between the rth order moments obtained from the SHS framework and the joint probability distribution of r noninteracting particles walking in the same switching environment, which evolves according to a QBPD. This result is reminiscent of the Feynman–Kac-type formula obtained in [6].

There are a number of possible extensions of this work. In terms of applications, the more physically relevant generalization of the model used in [8] consists of a dynamic gate between every confinement domain, which are now distributed on a two-dimensional lattice. We have focused on a single dynamic gate because our goal is to demonstrate the utility of the SHS formulation by looking at the simple problem of how a single dynamic gate affects the statistics of a random walker. From a mathematical perspective, it would be interesting to study more general switching environments with many states and to solve the general inverse problem of determining the switching environment based on time series data from the BDP. Another possible application of our analytical framework is to the study of gene networks operating in a randomly switching environment [18, 30, 16]. The control of transcription (switching on or off of a gene) is mediated by proteins known as transcription factors. These bind to a promoter region along the DNA, and either initiate or terminate transcription of mRNA. Whether or not a promoter site is occupied may depend on the state of the environment, which will be common to all cells evolving in the same environment. 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. Thus the analogue of the position n of a random walker is the number of proteins synthesized by a gene regulatory network, and the analogue of a switching gate is a switching promoter site with discrete states $s(t)$.

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