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Global density equations for a population of actively switching particles

Paul C Bressloff

Department of Mathematics, Imperial College London, London SW7 2AZ, United Kingdom

E-mail: p.bressloff@imperial.ac.uk

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Abstract

There are many processes in cell biology that can be modelled in terms of an actively switching particle. The continuous degrees of freedom of the particle evolve according to a hybrid stochastic differential equation whose drift term depends on a discrete internal or environmental state that switches according to a continuous time Markov chain. Examples include Brownian motion in a randomly switching environment, membrane voltage fluctuations in neurons, protein synthesis in gene networks, bacterial run-and-tumble motion, and motor-driven intracellular transport. In this paper we derive generalized Dean–Kawasaki (DK) equations for a population of actively switching particles, either independently switching or subject to a common randomly switching environment. In the case of a random environment, we show that the global particle density evolves according to a hybrid DK equation. Averaging with respect to the Gaussian noise processes in the absence of particle interactions yields a hybrid partial differential equation for the one-particle density. We use this to show how a randomly switching environment induces statistical correlations between the particles. We also discuss methods for handling the moment closure problem for interacting particles, including dynamical density functional theory and mean field theory. We then develop the analogous constructions for independently switching particles. In order to derive a DK equation, we introduce a discrete set of global densities that are indexed by the single-particle internal states, and take expectations with respect to the switching process. However, the resulting DK equation is no longer closed when

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particle interactions are included. We conclude by deriving Martin–Siggia–Rose–Janssen–de Dominicis path integrals for the global density equations in the absence of interactions, and relate this to recent field theoretic studies of Brownian gases and run-and-tumble particles.

Keywords: hybrid stochastic differential equations, active switching, statistical field theory, path integrals, Dean–Kawasaki equation

1. Introduction

There are a diverse range of processes in cell biology that can be modelled as an actively switching particle [1]. The continuous degrees of freedom of the particle evolve according to a hybrid stochastic differential equation (hSDE), whose drift term depends on a discrete state that switches according to a continuous time Markov chain. Let $(\mathbf{X}(t), N(t))$ denote the state of the system at time t with $\mathbf{X}(t) \in \mathbb{R}^d$ and $N(t) \in \Gamma$, where Γ is a discrete set. If $N(t) = n \in \Gamma$ then $\mathbf{X}(t)$ evolves according to the SDE $d\mathbf{X} = \mathbf{A}_n(\mathbf{X})dt + \sqrt{2D}d\mathbf{W}(t)$, where $\mathbf{W}(t)$ is a vector of independent Wiener processes and $\mathbf{A}_n$ is an n-dependent drift term. (For simplicity, we take the diffusivity to be independent of n.) Finally, the matrix generator $\mathbf{Q}$ of the continuous time Markov chain $N(t)$ may itself depend on $\mathbf{X}(t)$. In the limit $D \to 0$, the dynamics reduces to a so-called piecewise deterministic Markov process [2].

One well-known example of an hSDE arises within the context of membrane voltage fluctuations in a single neuron that are driven by the stochastic opening and closing of ion channels [3–10], see figure 1(a). The continuous variable $X(t) \in \mathbb{R}$ is the membrane voltage, whereas the discrete state $N(t)$ specifies the conformational states of the ion channels (and hence the ionic membrane currents). The ion channels evolve according to a continuous-time Markov process with voltage-dependent transition rates. Applying the law of large numbers in the thermodynamic limit recovers deterministic Hodgkin-Huxley type equations. On the other hand, in the case of a finite number of channels, noise-induced spontaneous firing of a neuron can occur due to channel fluctuations. Another example of an hSDE is a gene regulatory network, where $X(t)$ is the concentration of a protein product and the discrete variable represents the activation state of the gene [11–16], see figure 1(b). Stochastically switching between active and inactive gene states can result in translational/transcriptional bursting. Moreover, if switching persists at the phenotypic level then this provides certain advantages to cell populations growing in a changing environment, as exemplified by bacterial persistence in response to antibiotics. Yet another example is active intracellular transport on microtubular networks, where motor-cargo complexes randomly switch between different velocity states according to a special type of hSDE known as a velocity jump process [17–21], see figure 1(c). Velocity jump processes have also been used to model the 'run-and-tumble' swimming motion of bacteria such as *E. coli* [22–24]. This is characterized by periods of almost constant ballistic motion (runs), interrupted by sudden random changes in the direction of motion (tumbling), see figure 1(d). For velocity jump processes, $\mathbf{X}(t)$ represents the particle position and $N(t)$ specifies the velocity state.

In the above examples the stochastic variable $N(t)$ represents an internal or intrinsic state of the system. Another class of hybrid system is overdamped Brownian motion in a randomly switching environment, in which $\mathbf{X}(t)$ represents the spatial position of the particle at time t and $N(t)$ is the current environmental state. In particular, suppose that $\mathbf{A}_n(\mathbf{X}) = -\gamma^{-1}\boldsymbol{\nabla} V_n(\mathbf{X})$, where γ is a friction coefficient with $\gamma D = k_BT$ and $V_n(\mathbf{X})$ is an external potential. Switching

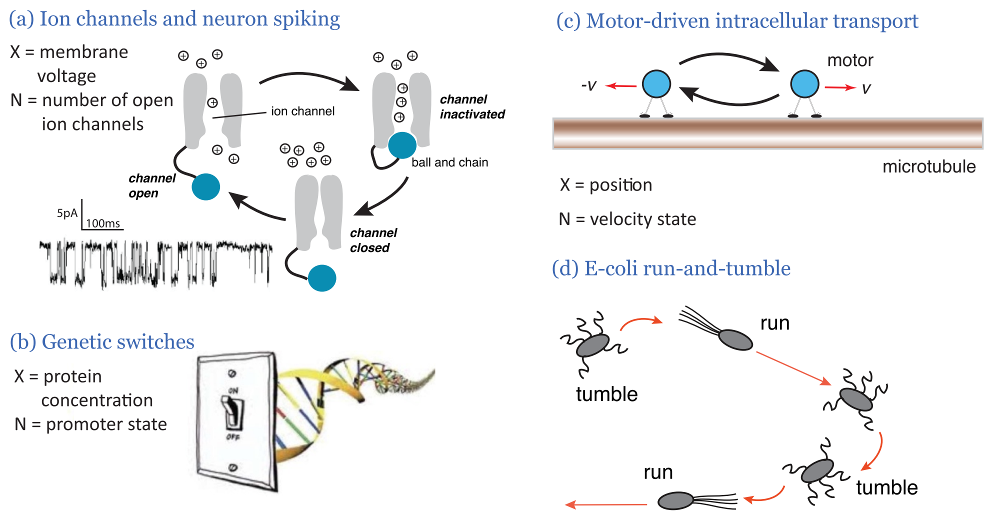

Figure 1. Examples of systems in cell biology modelled using hSDEs. (a) Ion channels. (b) Genetic switches. (c) Bidirectional motor transport. (d) Bacterial run-and-tumble.

between different environmental states results in the particle being driven by different external potentials. It is also possible to have a combination of environmental and intrinsic states. Examples include an external chemical gradient regulating the tumbling rate of a run-and-tumble particle (RTP) during chemotaxis [25, 26], an external electric field regulating the opening and closing of a neuron's ion channels, and phenotypic switching of bacterial populations in randomly switching environments [1]. Conversely, an overdamped Brownian particle can intrinsically switch between different conformational states. This may modify its effective diffusivity (possibly by temporarily binding to some some chemical substrate [27–29]) or how it interacts with other particles (as in the case of soft colloids [30, 31]). Mathematically speaking, at the single particle level, the analysis of an hSDE holds irrespective of whether $N(t)$ is interpreted as a discrete internal state (intrinsic switching) or an external environmental state (extrinsic switching). However, for a population of actively switching particles, the two scenarios differ significantly, even in the absence of particle-particle interactions.

In this paper, we explore the differences between intrinsic and extrinsic switching by considering a population of particles that either independently switch or are subject to a common randomly switching environment. (For simplicity, we assume throughout that the matrix generator $\mathbf{Q}$ is independent of $\mathbf{X}(t)$.) In both cases we derive 'hydrodynamic' evolution equations for the global particle density by extending the classical derivation of Dean [32], see also [33]. The Dean–Kawasaki (DK) equation for non-switching systems is a stochastic partial differential equation (SPDE) that describes fluctuations in the global density $\rho(\mathbf{x},t) = N^{-1}\sum_{j=1}^{N}\delta(\mathbf{x}-\mathbf{X}_j(t))$ of N over-damped Brownian particles (Brownian gas) with positions $\mathbf{X}_j(t)\in\mathbb{R}^d$ at time t [32, 33]. It is an exact equation for the global density in the distributional sense, and is of considerable current interest within the context of stochastic and numerical analysis [34–40]. The DK equation is also used extensively in non-equilibrium statistical physics, where it is combined with dynamical density functional theory (DDFT) in order to derive hydrodynamical models of interacting particle systems [41–44]. Such models arise in a

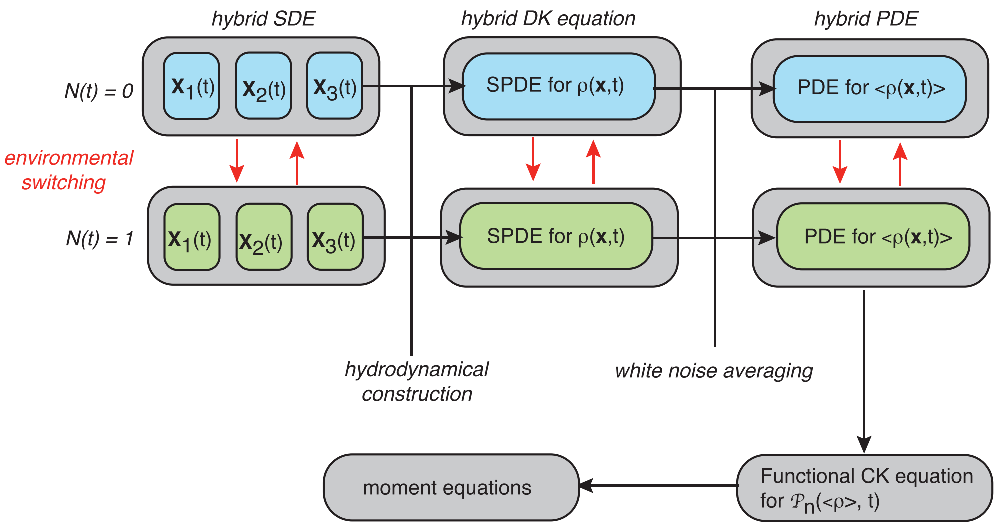

Figure 2. Hierarchy of model equations for the density function of a population of non-interacting particles in a randomly switching environment. (For the sake of illustration, we assume that there are two environmental states labelled $n = 0, 1$.) The hybrid DK equation has two sources of noise—Gaussian noise and environmental switching. Averaging with respect to the former results in a hybrid PDE for $u(\mathbf{x},t) = \langle \rho(\mathbf{x},t)\rangle$ that still depends on the random environmental state. This results in statistical correlations between the particles even in the absence of particle interactions, which can be shown by taking moments of the corresponding functional CK equation of the hybrid PDE. Particle interactions can be incorporated into the hybrid DK equation, but result in a moment closure problem when averaging with respect to the white noise.

variety of studies of active matter [45–49]. These focus on models of motile actively switching particles whose velocity state either randomly switches between different discrete states (run-and-tumble motion) or undergoes rotational diffusion (active Brownian motion). In the former case, a coarse-graining procedure is used to approximate the single-particle dynamics by a drift-diffusion process, which is then extended to multiple interacting particles. A major application of these studies is to motility-based phase separation [50].

We begin by briefly reviewing the case of a single actively switching particle, whose state $\mathbf{X}(t)$ evolves according to an hSDE with drift term $A_n(\mathbf{X}(t))$ that depends on the current discrete state $N(t)$ (section 2). We also write down the differential Chapman–Kolomogorov (CK) equation for the corresponding probability density $p_n(\mathbf{x},t)$, where $p_n(\mathbf{x},t)d\mathbf{x} = \mathbb{P}[\mathbf{X}(t) \in [\mathbf{x},\mathbf{x}+d\mathbf{x}], N(t) = n]$. In section 3, we consider a population of identical, non-interacting particles subject to a common randomly switching environment. We first derive a hybrid DK equation for the global density $\rho(\mathbf{x},t) = \sum_j \delta(\mathbf{X}_j(t) - \mathbf{x})$, where $\mathbf{X}_j(t) \in \mathbb{R}^d$ is the position of the jth particle at time t. The hybrid DK equation has both Gaussian noise and discrete noise due to environmental switching. Averaging with respect to the former yields a hybrid PDE for $u(\mathbf{x},t) = \langle \rho(\mathbf{x},t)\rangle$ that still depends on the random environmental state. We use the corresponding functional CK equation to derive moment equations for the one-particle density, and thus show how a randomly switching environment induces statistical correlations. The various versions of the model equations for non-interacting particles with environmental switching are summarized in figure 2. We conclude section 3 by discussing methods for handling the

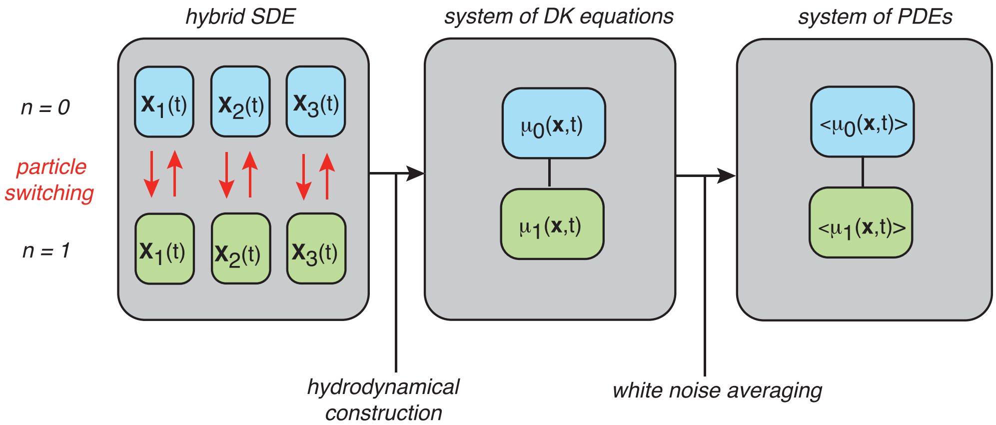

Figure 3. Corresponding hierarchy of model equations for the global density functions of a population of non-interacting particles that independently switch between different internal states. We now have a system of DK equations for the indexed global densities $\mu_n(\mathbf{x},t)$ that only has Gaussian noise. Averaging with respect to the latter results in a deterministic PDE, and hence there are no statistical correlations in the absence of particle interactions. Particle interactions can no longer be incorporated into the system of DK equations, since taking expectations with respect to the switching processes results in a moment closure problem.

moment closure problem due to particle interactions, including hybrid versions of dynamical density functional theory and mean field theory. In section 4, we develop the analogous theory for a population of independently switching particles. We now introduce an indexed set of global densities defined according to $\mu_n(\mathbf{x},t) = \sum_j \delta(\mathbf{X}_j(t) - \mathbf{x})\mathbb{E}[\delta_{N_j(t)=n}]$, where $N_j(t)$ is the discrete state of the jth particle at time t and expectation is taken with respect to the continuous time Markov chain. This allows us to derive a closed system of DK equations for the densities $\mu_n(\mathbf{x},t)$ in the absence of particle interactions. The various versions of the model equations for non-interacting particles with intrinsic switching are summarized in figure 3. However, it is no longer possible to obtain closed DK equations when particle interactions are included, since averaging with respect to the switching process results in a moment closure problem. One way to handle the latter is to take expectations with respect to the switching and Gaussian noise processes and applying a mean field ansatz. Finally, in section 5 we derive Martin–Siggia–Rose–Janssen–de Dominicis (MSRJD) functional path integrals for the DK equations in the case of non-interacting particles. Again, we emphasize the differences between environmental and intrinsic switching.

2. Single actively switching particle

Consider a particle whose states are described by a pair of stochastic variables $(\mathbf{X}(t), N(t)) \in \mathbb{R}^d \times \{0,\ldots,K-1\}$. When the discrete state is $N(t) = n$, the particle evolves according to the SDE

$$d\mathbf{X}(t) = \mathbf{A}_n(\mathbf{X}(t))\,dt + \sqrt{2D}d\mathbf{W}(t), \tag{2.1}$$

where $\mathbf{W}$ is a vector of d independent Wiener processes. The discrete stochastic variable $N(t)$ evolves according to a K-state continuous-time Markov chain with a $K \times K$ matrix generator $\mathbf{Q}$ that is taken to be independent of $\mathbf{X}(t)$. It is related to the corresponding transition matrix $\mathbf{T}$ according to

$$Q_{nm} = T_{nm} - \delta_{n,m} \sum_{k=0}^{K-1} T_{km}. \tag{2.2}$$

We also assume that the generator is irreducible so that there exists a stationary density $\boldsymbol{\sigma}$ for which $\sum_m Q_{nm}\sigma_m = 0$. Given the initial conditions $\mathbf{X}(0) = \mathbf{x}_0, N(0) = n_0$, we introduce the probability density $p_n(\mathbf{x}, t|\mathbf{x}_0, n_0, 0)$ with

$$\mathbb{P}\left[\mathbf{X}(t) \in [\mathbf{x}, \mathbf{x} + d\mathbf{x}], N(t) = n|\mathbf{x}_0, n_0\right] = p_n(\mathbf{x}, t|\mathbf{x}_0, n_0, 0)\, d\mathbf{x}.$$

It can be shown that p evolves according to the forward differential CK equation [1, 51]

$$\frac{\partial p_n}{\partial t} = -\nabla \cdot [\mathbf{A}_n(\mathbf{x}) p_n(\mathbf{x}, t)] + D\boldsymbol{\nabla}^2 p_n(\mathbf{x}, t) + \sum_{m=0}^{K-1} Q_{nm} p_m(\mathbf{x}, t). \tag{2.3}$$

(For notational convenience we have dropped the explicit dependence on initial conditions.) The first two terms on the right-hand side represent the probability flow associated with the SDE for a given n, whereas the third term represents jumps in the discrete state n.

In the case of the hSDE (2.1) for the pair $(\mathbf{X}(t), N(t))$, the stochastic dynamics is the same whether $N(t)$ is interpreted as a discrete internal state or an external environmental state. However, for a population of non-interacting actively switching particles, the two scenarios differ significantly. First, suppose that there are $\mathcal{N}$ particles with continuous states $\mathbf{X}_j(t)$, $j = 1, \ldots, \mathcal{N}$, and subject to independent white noise processes $\mathbf{W}_j(t)$. If each particle has its own internal state $N_j(t)$, then the population version of equation (2.1) is

$$d\mathbf{X}_j(t) = \mathbf{A}_{n_j}(\mathbf{X}_j(t))\, dt + \sqrt{2D} d\mathbf{W}_j(t), \quad N_j(t) = n_j. \tag{2.4}$$

We can treat the full system as the product of $\mathcal{N}$ independent hSDEs $(\mathbf{X}_j(t), N_j(t))$ (assuming that the initial conditions are also independent). On the other hand, if each particle is subject to the same discrete environmental state $N(t)$ then

$$d\mathbf{X}_j(t) = \mathbf{A}_n(\mathbf{X}_j(t))\, dt + \sqrt{2D} d\mathbf{W}_j(t), \quad N(t) = n. \tag{2.5}$$

Since $N(t)$ is a global variable that is experienced by all members of the population, it follows that the particles are statistically correlated, even in the absence of particle-particle interactions. One way to interpret equation (2.5) is as a single hSDE for the high-dimensional system $(\mathbf{Z}(t), N(t))$ with $\mathbf{Z}(t) = (\mathbf{X}_1(t), \ldots, \mathbf{X}_{\mathcal{N}}(t))$. The corresponding CK equation for the probability density $\mathcal{P}_n(\mathbf{z}, t)$ takes the form

$$\frac{\partial \mathcal{P}_n}{\partial t} = -\sum_{j=1}^{\mathcal{N}} \nabla_j \cdot [\mathbf{A}_n(\mathbf{x}_j) \mathcal{P}_n(\mathbf{z}, t)] + D \sum_{j=1}^{\mathcal{N}} \nabla_j^2 \mathcal{P}_n(\mathbf{z}, t) + \sum_{m=0}^{K-1} Q_{nm} \mathcal{P}_m(\mathbf{z}, t), \tag{2.6}$$

where $\mathbf{z} = (\mathbf{x}_1, \ldots, \mathbf{x}_{\mathcal{N}})$, $\nabla_j = \nabla_{\mathbf{x}_j}$ and $N(t) = n$. The presence of the final term on the right-hand side means that we cannot factorize the solution according to $\mathcal{P}_n(\mathbf{z}, t) = \prod_{j=1}^{\mathcal{N}} P_n(\mathbf{x}_j, t)$, where $P_n(\mathbf{x}, t)$ satisfies the CK equation (2.3). This reflects the existence of statistical correlations. In the following sections we explore these differences in terms of hydrodynamical equations for the global particle density.

3. Population of particles with environmental switching

3.1. Global density (non-interacting particles)

Consider a population of non-interacting particles in the presence of a randomly switching environment. A typical example would be a population of overdamped Brownian particles subject to a common randomly switching external potential. A more compact description of the population dynamics of equation (2.5) can be obtained by considering a 'hydrodynamic' formulation that involves the global density

$$\rho(\mathbf{x},t) = \sum_{j=1}^{\mathcal{N}} \rho_j(\mathbf{x},t), \quad \rho_j(\mathbf{x},t) = \delta(\mathbf{X}_j(t) - \mathbf{x}). \tag{3.1}$$

In particular, following along identical lines to Dean [32], we can derive an Itô SPDE for $\rho(\mathbf{x},t)$ that depends on the environmental state via the drift vector $\mathbf{A}_{N(t)}$. For completeness, we sketch the basic steps. Suppose that at time t the environmental state is $N(t)$. Consider an arbitrary smooth function $f: \mathbb{R}^d \to \mathbb{R}$. Using Itô's lemma to Taylor expand $f(\mathbf{X}_i(t+dt))$ about $\mathbf{X}_i(t)$ and setting $f(\mathbf{X}_i(t)) = \int_{\mathbb{R}^d} \rho_i(\mathbf{x},t) f(\mathbf{x}) d\mathbf{x}$, we find that

$$\begin{aligned}\frac{df(\mathbf{X}_i)}{dt} &= \int_{\mathbb{R}^d} d\mathbf{x} f(\mathbf{x}) \frac{\partial \rho_i(\mathbf{x},t)}{\partial t} \\ &= \int_{\mathbb{R}^d} d\mathbf{x} \rho_i(\mathbf{x},t) \left[\sqrt{2D}\boldsymbol{\nabla} f(\mathbf{x}) \cdot \boldsymbol{\xi}_i(t) + D\boldsymbol{\nabla}^2 f(\mathbf{x}) + \boldsymbol{\nabla} f(\mathbf{x}) \cdot \mathbf{A}_{N(t)}(\mathbf{x})\right].\end{aligned} \tag{3.2}$$

We have formally set $d\mathbf{W}_i(t) = \boldsymbol{\xi}_i(t)dt$ where $\boldsymbol{\xi}_i$ is a d-dimensional white noise term such that

$$\langle \boldsymbol{\xi}_i(t) \rangle = 0, \quad \langle \xi_i^{\sigma}(t) \xi_j^{\sigma'}(t') \rangle = \delta(t-t') \delta_{i,j} \delta_{\sigma,\sigma'}. \tag{3.3}$$

Integrating by parts the various terms on the second line and using the fact that f is arbitrary yields a PDE for ρ_i:

$$\frac{\partial \rho_i(\mathbf{x},t)}{\partial t} = -\sqrt{2D}\boldsymbol{\nabla} \cdot [\rho_i(\mathbf{x},t)\boldsymbol{\xi}_i(t)] + D\boldsymbol{\nabla}^2 \rho_i(\mathbf{x},t) - \boldsymbol{\nabla} \cdot \left[\rho_i(\mathbf{x},t)\mathbf{A}_{N(t)}(\mathbf{x})\right]. \tag{3.4}$$

Summing over the particle index i and using the definition of the global density then gives

$$\frac{\partial \rho(\mathbf{x},t)}{\partial t} = -\sqrt{2D}\sum_{i=1}^{\mathcal{N}} \boldsymbol{\nabla} \cdot [\rho_i(\mathbf{x},t)\boldsymbol{\xi}_i(t)] + D\boldsymbol{\nabla}^2 \rho(\mathbf{x},t) - \boldsymbol{\nabla} \cdot \left[\rho(\mathbf{x},t)\mathbf{A}_{N(t)}(\mathbf{x})\right]. \tag{3.5}$$

As it stands, equation (3.5) is not a closed equation for ρ due to the noise terms. Following [32], we introduce the space-dependent Gaussian noise term

$$\xi(\mathbf{x},t) = -\sum_{i=1}^{\mathcal{N}} \boldsymbol{\nabla} \cdot [\rho_i(\mathbf{x},t)\boldsymbol{\xi}_i(t)] \tag{3.6}$$

with zero mean and the correlation function

$$\langle \xi(\mathbf{x},t) \xi(\mathbf{y},t') \rangle = \delta(t-t') \sum_{i=1}^{\mathcal{N}} \boldsymbol{\nabla}_{\mathbf{x}} \cdot \boldsymbol{\nabla}_{\mathbf{y}} (\rho_i(\mathbf{x},t)\rho_i(\mathbf{y},t)). \tag{3.7}$$

Since $\rho_i(\mathbf{x},t)\rho_i(\mathbf{y},t) = \delta(\mathbf{x}-\mathbf{y})\rho_i(\mathbf{y},t)$, it follows that

$$\langle \xi(\mathbf{x},t)\xi(\mathbf{y},t')\rangle = \delta(t-t')\boldsymbol{\nabla}_{\mathbf{x}}\cdot\boldsymbol{\nabla}_{\mathbf{y}}(\delta(\mathbf{x}-\mathbf{y})\rho(\mathbf{x},t)). \tag{3.8}$$

Finally, we introduce the global density-dependent noise field

$$\widehat{\xi}(\mathbf{x},t) = \boldsymbol{\nabla}\cdot(\eta(\mathbf{x},t)\sqrt{\rho}(\mathbf{x},t)), \tag{3.9}$$

where $\eta(\mathbf{x},t)$ is a global white noise field whose components satisfy

$$\langle \eta^{\sigma}(\mathbf{x},t)\eta^{\sigma'}(\mathbf{y},t')\rangle = \delta(t-t')\delta(\mathbf{x}-\mathbf{y})\delta_{\sigma,\sigma'}. \tag{3.10}$$

It can be checked that the Gaussian noises ξ and $\widehat{\xi}$ have the same correlation functions and are thus statistically identical. We thus obtain a closed hSPDE for the global density that couples to the environmental state $N(t)$:

$$\frac{\partial\rho(\mathbf{x},t)}{\partial t} = \sqrt{2D}\boldsymbol{\nabla}\cdot\left[\sqrt{\rho(\mathbf{x},t)}\boldsymbol{\eta}(\mathbf{x},t)\right] + D\boldsymbol{\nabla}^2\rho(\mathbf{x},t) - \boldsymbol{\nabla}\cdot\left[\rho(\mathbf{x},t)\mathbf{A}_{N(t)}(\mathbf{x})\right]. \tag{3.11}$$

Note that the $N(t)$-dependence of the drift vector $\mathbf{A}_{N(t)}$ introduces another level of stochasticity due to the randomly switching environment. As we show below, this introduces statistical correlations between the particles. On the other hand, if the drift term is independent of the environmental state, then statistical correlations will only occur if there are particle-particle interactions [32], see also section 3.3. We refer to equation (3.11) as a hybrid DK equation for the global density $\rho(\mathbf{x},t)$.

3.2. Statistical correlations and moment equations for the one-body density

In order to investigate statistical correlations induced by the random environment, we average the hSPDE (3.11) with respect to the independent Gaussian noise terms to obtain a closed hPDE for the one-body density

$$u(\mathbf{x},t) = \langle\rho(\mathbf{x},t)\rangle. \tag{3.12}$$

(If pairwise particle interactions were included then $\langle\rho(\mathbf{x},t)\rangle$ would couple to the second order moment $\langle\rho(\mathbf{x},t)\rho(\mathbf{y},t)\rangle$ etc. Hence, moment closure would no longer hold [32], see below.) Between jumps in the environmental state, the density $u(\mathbf{x},t)$ evolves according to the drift-diffusion equation

$$\frac{\partial u(\mathbf{x},t)}{\partial t} = D\boldsymbol{\nabla}^2 u(\mathbf{x},t) - \boldsymbol{\nabla}\cdot\left(u(\mathbf{x},t)\mathbf{A}_{N(t)}(\mathbf{x})\right). \tag{3.13}$$

This type of stochastic hybrid model can be analyzed along similar lines to reaction-diffusion equations with randomly switching boundaries [52–54]. We proceed by spatially discretizing equation (3.13) in terms of a d-dimensional regular lattice with nodes $\boldsymbol{\ell}\in\mathbb{Z}^d$ and lattice spacing h. Let $\Gamma_{\boldsymbol{\ell}}$ denote the set of nearest neighbours of $\boldsymbol{\ell}$:

$$\Gamma_{\boldsymbol{\ell}} = \{\boldsymbol{\ell}\pm\mathbf{e}_{\sigma}, \sigma = 1,\dots d\}, \tag{3.14}$$

where $\mathbf{e}_\sigma$ is the unit vector along the σ-axis. Setting $u_{\boldsymbol{\ell}}(t) = u(\boldsymbol{\ell}h, t)$ and $A^\sigma_{n,\boldsymbol{\ell}} = A^\sigma_n(\boldsymbol{\ell}h)$, $\boldsymbol{\ell} \in \mathbb{Z}^d$, we obtain the piecewise deterministic ODE

$$\frac{du_{\boldsymbol{\ell}}}{dt} = D\left[\Delta(\mathbf{u})\right]_{\boldsymbol{\ell}} - \frac{1}{h}\sum_{\sigma=1}^{d}\left[u_{\boldsymbol{\ell}+\mathbf{e}_\sigma}A^\sigma_{n,\boldsymbol{\ell}+\mathbf{e}_\sigma} - u_{\boldsymbol{\ell}}A^\sigma_{n,\boldsymbol{\ell}}\right], \tag{3.15}$$

where $N(t) = n$ and Δ is the discrete Laplacian

$$\left[\Delta(\mathbf{u})\right]_{\boldsymbol{\ell}} = \frac{1}{h^2}\sum_{\boldsymbol{\ell}'\in\Gamma_{\boldsymbol{\ell}}}\left[u_{\boldsymbol{\ell}'} - u_{\boldsymbol{\ell}}\right]. \tag{3.16}$$

Introducing the infinite-dimensional vector $\mathbf{U} = (u_{\boldsymbol{\ell}}, \boldsymbol{\ell} \in \mathbb{Z}^d)$ and the corresponding probability density

$$\mathcal{P}_n(\mathbf{u}, t)\, d\mathbf{u} = \mathbb{P}\left\{\mathbf{U}(t) \in [\mathbf{u}, \mathbf{u} + d\mathbf{u}], N(t) = n\right\}, \tag{3.17}$$

we write down the following CK equation for the spatially discretized system:

$$\begin{aligned}\frac{\partial \mathcal{P}_n}{\partial t} = &-\sum_{\boldsymbol{\ell}\in\mathbb{Z}^d}\frac{\partial}{\partial u_{\boldsymbol{\ell}}}\left[\left(D\left[\Delta(\mathbf{u})\right]_{\boldsymbol{\ell}} - \frac{1}{h}\sum_{\sigma=1}^{d}\left[u_{\boldsymbol{\ell}+\mathbf{e}_\sigma}A^\sigma_{n,\boldsymbol{\ell}+\mathbf{e}_\sigma} - u_{\boldsymbol{\ell}}A^\sigma_{n,\boldsymbol{\ell}}\right]\right)\mathcal{P}_n(\mathbf{u}, t)\right] \\ &+ \sum_m Q_{nm}\mathcal{P}_m(\mathbf{u}, t).\end{aligned} \tag{3.18}$$

Finally, we take the continuum limit $h \to 0$ of equation (3.18). This yields a functional CK equation for the many-body probability functional $\mathcal{P}_n[u, t]$ with

$$\mathcal{P}_n[u, t]\prod_{\mathbf{x}} du(\mathbf{x}) = \lim_{h\to 0}\mathcal{P}_n(\mathbf{u}, t)\, d\mathbf{u}. \tag{3.19}$$

That is,

$$\begin{aligned}\frac{\partial \mathcal{P}_n[u, t]}{\partial t} = &-\int_{\mathbb{R}^d} d\mathbf{x}\,\frac{\delta}{\delta u(\mathbf{x})}\left[\left(D\boldsymbol{\nabla}^2 u(\mathbf{x}) - \boldsymbol{\nabla}\cdot\left[u(\mathbf{x})\mathbf{A}_n(\mathbf{x})\right]\right)\mathcal{P}_n[u, t]\right] \\ &+ \sum_m Q_{nm}\mathcal{P}_m[u, t].\end{aligned} \tag{3.20}$$

Equation (3.20) can now be used to derive various moment equations. For example, the first moment is defined as

$$\mathcal{U}_n(\mathbf{x}_1, t) \equiv \mathbb{E}\left[u(\mathbf{x}_1, t)\, 1_{N(t)=n}\right] = \int \mathcal{D}[u]\, u(\mathbf{x}_1)\,\mathcal{P}_n[u, t]. \tag{3.21}$$

We take $\mathbb{E}[\cdot]$ to denote expectation with respect to the switching process in order to contrast it with $\langle\cdot\rangle$, which denotes averaging with respect to the Gaussian noise, that is, $u(\mathbf{x}, t) = \langle\rho(\mathbf{x}, t)\rangle$ etc. Also note that in the final functional integral the time-dependence is specified by the many-body probability functional $\mathcal{P}_n[u, t]$. Multiplying both sides of equation (3.20) by $u(\mathbf{x}_1)$ and functionally integrating with respect to u gives

$$\frac{\partial}{\partial t}\int \mathcal{D}[u]\,u(\mathbf{x}_1)\,\mathcal{P}_n[u,t] = -\int \mathcal{D}[u]\,u(\mathbf{x}_1)\left\{\int_{\mathbb{R}^d} d\mathbf{x}\,\frac{\delta}{\delta u(\mathbf{x})}\left[\left(D\boldsymbol{\nabla}^2 u(\mathbf{x}) - \boldsymbol{\nabla}\cdot\left[u(\mathbf{x})\,\mathbf{A}_n(\mathbf{x})\right]\right)\mathcal{P}_n[u,t]\right] + \sum_m Q_{nm}\mathcal{P}_m[u,t]\right\}. \quad (3.22)$$

Functionally integrating by parts and using the functional derivative identity $\delta u(\mathbf{x}_1)/\delta u(\mathbf{x}) = \delta(\mathbf{x}-\mathbf{x}_1)$, we have

$$\frac{\partial}{\partial t}\int \mathcal{D}[u]\,u(\mathbf{x}_1)\,\mathcal{P}_n[u,t] = \int \mathcal{D}[u]\left\{\left[\left(D\boldsymbol{\nabla}_1^2 u(\mathbf{x}_1) - \boldsymbol{\nabla}_1\cdot\left[u(\mathbf{x}_1)\,\mathbf{A}_n(\mathbf{x}_1)\right]\right)\mathcal{P}_n[u,t]\right] + \sum_m Q_{nm}\mathcal{P}_m[u,t]\right\}, \quad (3.23)$$

which is equivalent to the first moment equation

$$\frac{\partial \mathcal{U}_n}{\partial t} = D\boldsymbol{\nabla}_1^2\mathcal{U}_n(\mathbf{x}_1,t) - \boldsymbol{\nabla}_1\cdot\left[\mathcal{U}_n(\mathbf{x}_1,t)\,\mathbf{A}_n(\mathbf{x}_1)\right] + \sum_m Q_{nm}\mathcal{U}_m(\mathbf{x}_1,t). \quad (3.24)$$

Note that equation (3.24) is identical to the CK equation (2.3) for the single particle hSDE (2.1) under the mapping $\mathcal{P}_n(\mathbf{x},t)\to\mathcal{U}_n(\mathbf{x},t) = \mathcal{N}\mathcal{P}_n(\mathbf{x},t)$. On the other hand, the second-order moments

$$C_n(\mathbf{x}_1,\mathbf{x}_2,t) = \mathbb{E}\left[u(\mathbf{x}_1,t)\,u(\mathbf{x}_2,t)\,1_{N(t)=n}\right]. \quad (3.25)$$

evolve according to the equation

$$\frac{\partial C_n}{\partial t} = D\boldsymbol{\nabla}_1^2 C_n(\mathbf{x}_1,\mathbf{x}_2,t) + D\boldsymbol{\nabla}_2^2 C_n(\mathbf{x}_1,\mathbf{x}_2,t) - \boldsymbol{\nabla}_1\cdot\left[C_n(\mathbf{x}_1,\mathbf{x}_2,t)\,\mathbf{A}_n(\mathbf{x}_1)\right] - \boldsymbol{\nabla}_2\cdot\left[C_n(\mathbf{x}_1,\mathbf{x}_2,t)\,\mathbf{A}_n(\mathbf{x}_2)\right] + \sum_m Q_{nm}C_m(\mathbf{x}_1,\mathbf{x}_2,t). \quad (3.26)$$

The latter can be derived from equation (3.20) after multiplying both sides by the product $u(\mathbf{x}_1)u(\mathbf{x}_2)$ and functionally integrating by parts along similar lines to the first moments. Interestingly, the second moment equation (3.26) takes the form of a CK equation for an effective single particle hSDE with $2d$ continuous coordinates $(\mathbf{X}(t),\mathbf{Y}(t))$: if $N(t) = n$ then

$$d\mathbf{X}(t) = \mathbf{A}_n(\mathbf{X}(t))\,dt + \sqrt{2D}d\mathbf{W}_1(t), \quad (3.27a)$$

$$d\mathbf{Y}(t) = \mathbf{A}_n(\mathbf{Y}(t))\,dt + \sqrt{2D}d\mathbf{W}_2(t), \quad (3.27b)$$

where $(\mathbf{W}_1,\mathbf{W}_2)^\top$ is a vector of $2d$ independent Wiener processes.

One of the major implications of the moment equations is that the common randomly switching environment introduces statistical correlations between the particles, even in the absence of particle interactions. For example, the two-point correlation function is non-zero since $C_n(\mathbf{x}_1,\mathbf{x}_2,t)\neq\mathcal{U}_n(\mathbf{x}_1,t)\mathcal{U}_n(\mathbf{x}_2,t)$. We establish the latter using proof by contradiction. Suppose that $C_n(\mathbf{x}_1,\mathbf{x}_2,t) = \mathcal{U}_n(\mathbf{x}_1,t)\mathcal{U}_n(\mathbf{x}_2,t)$. Substituting this trial solution into equation (3.26) gives

$$\begin{aligned}
&\mathcal{U}_n(\mathbf{x}_2,t)\frac{\partial \mathcal{U}_n(\mathbf{x}_1,t)}{\partial t}+\mathcal{U}_n(\mathbf{x}_1,t)\frac{\partial \mathcal{U}_n(\mathbf{x}_2,t)}{\partial t} \\
&\quad = D\mathcal{U}_n(\mathbf{x}_2,t)\nabla_1^2\mathcal{U}_n(\mathbf{x}_1,t)+D\mathcal{U}_n(\mathbf{x}_1,t)\nabla_2^2\mathcal{U}_n(\mathbf{x}_2,t)-\mathcal{U}_n(\mathbf{x}_2,t)\nabla_1\cdot[\mathcal{U}_n(\mathbf{x}_1,t)\mathbf{A}_n(\mathbf{x}_1)] \\
&\qquad -\mathcal{U}_n(\mathbf{x}_1,t)\nabla_2\cdot[\mathcal{U}_n(\mathbf{x}_2,t)\mathbf{A}_n(\mathbf{x}_2)]+\sum_m Q_{nm}\mathcal{U}_m(\mathbf{x}_1,t)\mathcal{U}_m(\mathbf{x}_2,t).
\end{aligned}$$

Applying the first moment equation (3.24) then implies that

$$\begin{aligned}
0 &= \mathcal{U}_n(\mathbf{x}_2,t)\sum_m Q_{nm}\mathcal{U}_m(\mathbf{x}_1,t)+\mathcal{U}_n(\mathbf{x}_1,t)\sum_m Q_{nm}\mathcal{U}_m(\mathbf{x}_2,t) \\
&\quad +\sum_m Q_{nm}\mathcal{U}_m(\mathbf{x}_1,t)\mathcal{U}_m(\mathbf{x}_2,t),
\end{aligned}$$

which is clearly false. Hence, $C_n(\mathbf{x}_1,\mathbf{x}_2,t)\neq\mathcal{U}_n(\mathbf{x}_1,t)\mathcal{U}_n(\mathbf{x}_2,t)$. Similar results hold for higher-order moments.

3.3. Interacting Brownian particles and mean field theory

So far we have ignored the effects of particle interactions. In the case of overdamped Brownian particles, such interactions are typically taken to be pairwise so that equation (2.5) becomes

$$d\mathbf{X}_j(t)=\left[\mathbf{A}_{N(t)}(\mathbf{X}_j(t))+\sum_{k=1}^{\mathcal{N}}\mathbf{F}(\mathbf{X}_j(t)-\mathbf{X}_k(t))\right]dt+\sqrt{2D}d\mathbf{W}_j(t). \tag{3.28}$$

If the forces are conservative, then $\mathbf{A}_n(\mathbf{x})=-\beta D\nabla V_n(\mathbf{x})$ and $\mathbf{F}(\mathbf{x})=-\beta D\nabla K(\mathbf{x})$, $\beta=1/k_BT$, where V_n is an environment-dependent potential and K is an interaction potential. The latter could also depend on the environmental state $N(t)$. The derivation of equation (3.11) can be extended to include particle interactions along analogous lines to [32]. The global density now evolves according to the hybrid DK equation

$$\begin{aligned}
\frac{\partial\rho(\mathbf{x},t)}{\partial t} &= \sqrt{2D}\nabla\cdot\left[\sqrt{\rho(\mathbf{x},t)}\boldsymbol{\eta}(\mathbf{x},t)\right]+D\nabla^2\rho(\mathbf{x},t) \\
&\quad -\nabla\cdot\rho(\mathbf{x},t)\left(\mathbf{A}_{N(t)}(\mathbf{x})+\int_{\mathbb{R}^d}\rho(\mathbf{y},t)\mathbf{F}(\mathbf{x}-\mathbf{y})\,d\mathbf{y}\right).
\end{aligned} \tag{3.29}$$

When particle interactions are included, averaging equation (3.29) with respect to the Gaussian noise no longer generates a closed equation for $u(\mathbf{x},t)=\langle\rho(\mathbf{x},t)\rangle$:

$$\begin{aligned}
\frac{\partial u(\mathbf{x},t)}{\partial t} &= D\nabla^2 u(\mathbf{x},t)-\nabla\cdot\left[u(\mathbf{x},t)\mathbf{A}_{N(t)}(\mathbf{x})\right] \\
&\quad -\nabla\cdot\int_{\mathbb{R}^d}\langle\rho(\mathbf{x},t)\rho(\mathbf{y},t)\rangle\mathbf{F}(\mathbf{x}-\mathbf{y})\,d\mathbf{y}.
\end{aligned} \tag{3.30}$$

That is, $u(\mathbf{x},t)$ couples to the two-point correlation function

$$u^{(2)}(\mathbf{x},\mathbf{y},t)=\langle\rho(\mathbf{x},t)\rho(\mathbf{y},t)\rangle, \tag{3.31}$$

which, in turn, depends on the three-point correlation function etc.

One way to achieve moment closure for the one-body density is to use DDFT [41–44]. A crucial assumption of DDFT is that the relaxation of the system is sufficiently slow such that the pair correlation can be equated with that of a corresponding equilibrium system at each point in time [44]. This allows one to approximate equation (3.30) by the closed hPDE

$$\frac{\partial u(\mathbf{x},t)}{\partial t} = -\boldsymbol{\nabla}\cdot\mathbf{J}_n(\mathbf{x},t), \quad N(t)=n \tag{3.32}$$

where

$$\mathbf{J}_n(\mathbf{x},t) = -D\left\{\boldsymbol{\nabla}u(\mathbf{x},t)+\beta u(\mathbf{x},t)\boldsymbol{\nabla}\left[V_n(\mathbf{x})+\mu^{\mathrm{ex}}(\mathbf{x},t)\right]\right\}. \tag{3.33}$$

Here

$$\mu^{\mathrm{ex}}(\mathbf{x},t) = \frac{\delta F^{\mathrm{ex}}[u(\mathbf{x},t)]}{\delta u(\mathbf{x},t)}, \tag{3.34}$$

and $F^{\mathrm{ex}}[u]$ is the equilibrium excess free energy functional with the equilibrium density profiles replaced by non-equilibrium ones. One of the features of DDFT is that $F^{\mathrm{ex}}[u]$ is independent of the actual external potential, and is thus independent of the environmental state. In order to apply DDFT, it is necessary to take account of the fact that there is another time-scale, namely, the rate of environmental switching. How this affects the validity of the adiabatic approximation remains to be determined, and is the subject of future work. Intuitively speaking, in the fast switching limit one could first average with respect to the switching process along analogous lines to previous studies of single particle hSDEs, and then apply DDFT. More specifically, suppose that there is a separation of time scales between the discrete and continuous processes, so that if t is the characteristic time-scale of the relaxation dynamics then ϵt is the characteristic time-scale of the Markov chain for some small positive parameter ϵ. We define the averaged vector field $\overline{A}:\mathbb{R}^d\rightarrow\mathbb{R}^d$ by

$$\overline{\mathbf{A}}(\mathbf{x}) = \sum_{m=0}^{K-1}\sigma_m\mathbf{A}_m(\mathbf{x}), \tag{3.35}$$

where σ_m is the stationary distribution of the Markov chain, that is, $\sum_m Q_{nm}\sigma_m = 0$. Intuitively speaking, one would expect the hSDE (3.28) to reduce to the non-hybrid SDE

$$d\mathbf{X}_j(t) = \overline{\mathbf{A}}(\mathbf{X}_j(t))\,dt + \sum_{k=1}^{\mathcal{N}}\mathbf{F}(\mathbf{X}_j(t)-\mathbf{X}_k(t)) + \sqrt{2D}d\mathbf{W}_j(t), \tag{3.36}$$

in the fast switching limit $\varepsilon\rightarrow 0$. This can be made precise in terms of a law of large numbers for stochastic hybrid systems [55–58]. On the other hand, in the slow switching limit one could apply DDFT for fixed $N(t)=n$ and then consider switching between the n-dependent 1-particle density equations. However, since the hPDE (3.32) for fixed n takes the form of a nonlinear Fokker–Planck equation, it is no longer possible to obtain closed moment equations using the corresponding functional CK equation for $\mathcal{P}_n[u,t]$. Even assuming that both limiting cases are well-posed, it is unclear what happens at intermediate switching rates.

An alternative way of deriving a closed hPDE for an effective one-particle density is to use mean field theory. In the case of non-switching, weakly-interacting Brownian particles, there is an extensive mathematical literature on the mean field limit (or propagation of chaos), see for example [59–62]. More specifically, suppose that both the external and interaction potentials are independent of the environmental state, and take $K = K_0/\mathcal{N}$ where K_0 is a smooth function. Equation (3.28) then takes the form

$$d\mathbf{X}_j(t) = -D\beta\boldsymbol{\nabla}V(\mathbf{X}_j(t))\,dt - \frac{D\beta}{\mathcal{N}}\sum_{k=1}^{\mathcal{N}}\boldsymbol{\nabla}K_0(\mathbf{X}_j(t)-\mathbf{X}_k(t)) + \sqrt{2D}d\mathbf{W}_j(t)\,. \tag{3.37}$$

Introducing the normalized global density (or empirical measure)

$$\rho_{\mathcal{N}}(\mathbf{x},t) = \frac{1}{\mathcal{N}}\sum_{j=1}^{\mathcal{N}}\delta(\mathbf{x}-\mathbf{X}_j(t))\,, \tag{3.38}$$

the classical DK equation becomes

$$\begin{aligned}\frac{\partial\rho_{\mathcal{N}}(\mathbf{x},t)}{\partial t} &= \sqrt{\frac{2D}{\mathcal{N}}}\boldsymbol{\nabla}\cdot\left[\sqrt{\rho_{\mathcal{N}}(\mathbf{x},t)}\boldsymbol{\eta}(\mathbf{x},t)\right] + D\boldsymbol{\nabla}^2\rho_{\mathcal{N}}(\mathbf{x},t)\\ &\quad + D\beta\boldsymbol{\nabla}\cdot\rho_{\mathcal{N}}(\mathbf{x},t)\left(\boldsymbol{\nabla}V(\mathbf{x}) + \int_{\mathbb{R}^d}\rho_{\mathcal{N}}(\mathbf{y},t)\,\boldsymbol{\nabla}K_0(\mathbf{x}-\mathbf{y})\,\mathrm{d}\mathbf{y}\right).\end{aligned} \tag{3.39}$$

Furthermore, suppose that the joint probability density at $t=0$ takes the product form

$$p(\mathbf{x}_1,\ldots,\mathbf{x}_{\mathcal{N}},0) = \prod_{j=1}^{\mathcal{N}}\rho_0(\mathbf{x}_j)\,. \tag{3.40}$$

It can then be proven that, as $\mathcal{N}\to\infty$, $\rho_{\mathcal{N}}$ converges in distribution to the solution ρ of the so-called McKean–Vlasov equation [63]

$$\frac{\partial\rho(\mathbf{x},t)}{\partial t} = D\boldsymbol{\nabla}^2\rho(\mathbf{x},t) + D\beta\boldsymbol{\nabla}\cdot\rho(\mathbf{x},t)\left(\boldsymbol{\nabla}V(\mathbf{x}) + \int_{\mathbb{R}^d}\rho(\mathbf{y},t)\,\boldsymbol{\nabla}K_0(\mathbf{x}-\mathbf{y})\,d\mathbf{y}\right), \tag{3.41}$$

with $\rho(\mathbf{x},0)=\rho_0(\mathbf{x})$. Recently, this classical result has been extended to the case of weakly-interacting Brownian particles in a common randomly switching environment [64].

4. Population of particles with intrinsic switching

4.1. Global density (non-interacting particles)

The derivation of an evolution equation for the global density differs significantly for a population of particles that independently switch between a set of internal states along the lines of equation (2.4). Examples include regulatory gene networks, run-and-tumble particles, soft colloids, and molecular motors. In contrast to the case of a randomly switching environment, it is necessary to keep track of the pair $(\mathbf{X}_j(t), N_j(t))$ for each particle. The appropriate global or empirical measure is now

$$\widehat{\mu}_n(\mathbf{x},t) = \sum_{j=1}^{\mathcal{N}}\widehat{\rho}_j(\mathbf{x},n,t) \equiv \sum_{j=1}^{\mathcal{N}}\delta(\mathbf{X}_j(t)-\mathbf{x})\,\delta_{N_j(t),n}. \tag{4.1}$$

In order to derive an equation for $\widehat{\mu}_n$, we introduce an arbitrary set of smooth functions $f_n(x)$ such that

$$f_{N_j(t)}\left(\mathbf{X}_j(t)\right) = \sum_{n=0}^{K-1} \int_{\mathbb{R}^d} \widehat{\rho}_j(\mathbf{x}, n, t) f_n(\mathbf{x})\, d\mathbf{x}. \tag{4.2}$$

We then note that

$$\begin{aligned} f_{N_i(t+\Delta t)}\left(\mathbf{X}_i(t+\Delta t)\right) &= \sum_{n=0}^{K-1} f_n\left(\mathbf{X}_i(t+\Delta t)\right) \delta_{n,N_i(t+\Delta t)} \\ &= \sum_{n=0}^{K-1} \left[f_n\left(\mathbf{X}_i(t)\right) + \boldsymbol{\nabla} f_n\left(\mathbf{X}_i(t)\right) \cdot \Delta\mathbf{X}_i(t) + O\left(\Delta\mathbf{X}_i(t)^2\right) \right] \delta_{n,N_i(t+\Delta t)}. \end{aligned} \tag{4.3}$$

Applying Itô's lemma and setting $\rho_j(\mathbf{x},t) = \delta(\mathbf{X}_j(t) - \mathbf{x})$, we have

$$\begin{aligned} & f_{N_i(t+\Delta t)}\left(\mathbf{X}_i(t+\Delta t)\right) \\ &\quad \approx \sum_{n=0}^{K-1} \delta_{n,N_i(t+\Delta t)} \int_{\mathbb{R}^d} d\mathbf{x}\, \rho_i(\mathbf{x},t) \left\{ f_n(\mathbf{x}) + \Delta t \left[\sqrt{2D} \boldsymbol{\nabla} f_n(\mathbf{x}) \cdot \boldsymbol{\xi}_i(t) + D \boldsymbol{\nabla}^2 f_n(\mathbf{x}) \right.\right. \\ &\qquad \left.\left. + \boldsymbol{\nabla} f_n(\mathbf{x}) \cdot \mathbf{A}_n(\mathbf{x}) \right] + O\left(\Delta t^2\right) \right\} \\ &\quad = f_{N_i(t)}\left(X_i(t)\right) \\ &\qquad + \Delta t \sum_{n=0}^{K-1} \int_{\mathbb{R}^d} d\mathbf{x}\, \widehat{\rho}_i(\mathbf{x}, n, t) \left[\sqrt{2D} \boldsymbol{\nabla} f_n(\mathbf{x}) \cdot \boldsymbol{\xi}_i(t) + D \boldsymbol{\nabla}^2 f_n(\mathbf{x}) + \boldsymbol{\nabla} f_n(\mathbf{x}) \cdot \mathbf{A}_n(\mathbf{x}) \right] \\ &\qquad + \sum_{n=0}^{K-1} \left[\delta_{n,N_i(t+\Delta t)} - \delta_{n,N_i(t)} \right] \int_{\mathbb{R}^d} d\mathbf{x}\, \rho_i(\mathbf{x},t) \left\{ f_n(\mathbf{x}) + O(\Delta t) \right\}. \end{aligned} \tag{4.4}$$

Rearranging this equation, dividing through by Δt and taking the limit $\Delta t \to 0$ gives

$$\begin{aligned} \frac{d f_{N_i(t)}\left(\mathbf{X}_i(t)\right)}{dt} &= \sum_{n=0}^{K-1} \int_{\mathbb{R}^d} d\mathbf{x}\, \widehat{\rho}_i(\mathbf{x}, n, t) \left[\sqrt{2D} \boldsymbol{\nabla} f_n(\mathbf{x}) \cdot \boldsymbol{\xi}_i(t) + D \boldsymbol{\nabla}^2 f_n(\mathbf{x}) \right. \\ &\qquad \left. + \boldsymbol{\nabla} f_n(\mathbf{x}) \cdot \mathbf{A}_n(\mathbf{x}) \right] + \lim_{\Delta t \to 0} \sum_{n=0}^{K-1} \frac{\delta_{n,N_i(t+\Delta t)} - \delta_{n,N_i(t)}}{\Delta t} \int_{\mathbb{R}^d} d\mathbf{x}\, \rho_i(\mathbf{x},t) f_n(\mathbf{x}). \end{aligned} \tag{4.5}$$

(Note that in order to average with respect to the switching process (see below), we do not simply write down the continuous time Itô formula.)

Substituting for $f_{N_i(t)}(\mathbf{X}_i(t))$ using equation (4.2), we then take expectations with respect to the Markov chain. Setting $\rho_j(\mathbf{x},n,t) = \mathbb{E}[\widehat{\rho}_j(\mathbf{x},n,t)]$, and using the fact that[1]

$$\mathbb{E}\left[\lim_{\Delta t\to 0}\frac{\delta_{n,N_i(t+\Delta t)}-\delta_{n,N_i(t)}}{\Delta t}\right] = \sum_{m=0}^{K-1} Q_{nm}\mathbb{E}\left[\delta_{m,N_i(t)}\right], \tag{4.6}$$

where $\mathbf{Q}$ is the matrix generator, we find that

$$\sum_{n=0}^{K-1}\int_{\mathbb{R}^d} d\mathbf{x} f_n(\mathbf{x})\frac{\partial \rho_i(\mathbf{x},n,t)}{\partial t} = \sum_{n=0}^{K-1}\int_{\mathbb{R}^d} d\mathbf{x}\,\rho_i(\mathbf{x},n,t)\left[\sqrt{2D}\boldsymbol{\nabla} f_n(\mathbf{x})\cdot\boldsymbol{\xi}_i(t) + D\boldsymbol{\nabla}^2 f_n(\mathbf{x})\right.$$
$$\left. + \boldsymbol{\nabla} f_n(\mathbf{x})\cdot\mathbf{A}_n(\mathbf{x})\right] + \sum_{m=0}^{K-1} Q_{mn}\int_{\mathbb{R}^d} d\mathbf{x}\,\rho_i(\mathbf{x},m,t) f_n(\mathbf{x}). \tag{4.7}$$

Integrating by parts the various terms on the right-hand side, and exploiting the arbitrariness of the functions f_n yields the following hSPDE:

$$\frac{\partial \rho_i(\mathbf{x},n,t)}{\partial t} = \int_{\mathbb{R}^d} d\mathbf{x}\left\{-\sqrt{2D}\boldsymbol{\nabla}\cdot\left[\rho_i(\mathbf{x},n,t)\boldsymbol{\xi}_i(t)\right] + D\boldsymbol{\nabla}^2\rho_i(\mathbf{x},n,t)\right.$$
$$\left. -\boldsymbol{\nabla}\cdot\left[\rho_i(\mathbf{x},n,t)\mathbf{A}_n(\mathbf{x})\right]\right\} + \sum_{m=0}^{K-1} Q_{nm}\rho_i(\mathbf{x},m,t). \tag{4.8}$$

Finally, summing over the particle index i and defining $\mu_n(\mathbf{x},t) = \mathbb{E}[\widehat{\mu}_n(\mathbf{x},t)] = \sum_{j=1}^{\mathcal{N}}\rho_j(\mathbf{x},n,t)$ gives

$$\frac{\partial \mu_n(\mathbf{x},t)}{\partial t} = -\sqrt{2D}\sum_{i=1}^{\mathcal{N}}\boldsymbol{\nabla}\cdot\left[\rho_i(\mathbf{x},n,t)\boldsymbol{\xi}_i(t)\right] + D\boldsymbol{\nabla}^2\mu_n(\mathbf{x},t) - \boldsymbol{\nabla}\cdot\left[\mu_n(\mathbf{x},t)\mathbf{A}_n(\mathbf{x})\right]$$
$$+\sum_{m=0}^{K-1} Q_{nm}\mu_m(\mathbf{x},t). \tag{4.9}$$

As in the analysis of environmental switching, see equation (3.5), we do not have a closed equation for μ_n. However, we can generalize the construction of [32] by explicitly taking into account the discrete index n. More specifically, we introduce the space-dependent Gaussian noise terms

$$\xi_n(\mathbf{x},t) = -\sum_{i=1}^{\mathcal{N}}\boldsymbol{\nabla}\cdot\left[\rho_i(\mathbf{x},n,t)\boldsymbol{\xi}_i(t)\right] \tag{4.10}$$

with zero mean and the correlation function

$$\langle \xi_n(\mathbf{x},t)\xi_m(\mathbf{y},t')\rangle = \delta(t-t')\sum_{i=1}^{\mathcal{N}}\boldsymbol{\nabla}_{\mathbf{x}}\cdot\boldsymbol{\nabla}_{\mathbf{y}}\left(\rho_i(\mathbf{x},n,t)\rho_i(\mathbf{y},m,t)\right). \tag{4.11}$$

[1] The numerator in equation (4.6) is equal to 1 if $N_i(t)\neq n$ and $N_i(t+\Delta t) = n$, that is, there is a transition $m\to n$ for some $m\neq n$ in the time interval $[t,t+\Delta t]$, which occurs with probability $T_{nm}\Delta t$. Similarly, it is equal to -1 if $N_i(t) = n$ and $N_i(t+\Delta t)\neq n$, that is, there is a transition $n\to m$ for some $m\neq n$ with probability $T_{mn}\Delta t$.

Since

$$\rho_i(\mathbf{x},n,t)\,\rho_i(\mathbf{y},m,t) = \delta(\mathbf{x}-\mathbf{X}_i(t))\,\delta(\mathbf{y}-\mathbf{X}_i(t))\,\mathbb{E}\left[\delta_{N_i(t),n}\right]\mathbb{E}\left[\delta_{N_i(t),m}\right] \\ = \delta(\mathbf{x}-\mathbf{y})\,\delta_{n,m}\rho_i(\mathbf{y},n,t), \tag{4.12}$$

it follows that

$$\langle \xi_n(\mathbf{x},t)\,\xi_m(\mathbf{y},t')\rangle = \delta_{n,m}\delta(t-t')\sum_{i=1}^{\mathcal{N}} \boldsymbol{\nabla}_{\mathbf{x}}\cdot\boldsymbol{\nabla}_{\mathbf{y}}\left(\delta(\mathbf{x}-\mathbf{y})\,\rho_i(\mathbf{x},n,t)\right). \tag{4.13}$$

Finally, we introduce the global density-dependent noise fields

$$\widehat{\xi}_n(\mathbf{x},t) = \boldsymbol{\nabla}\cdot\left(\boldsymbol{\eta}_n(\mathbf{x},t)\sqrt{\mu_n(\mathbf{x},t)}\right), \tag{4.14}$$

where $\eta_n(\mathbf{x},t)$ is a global white noise field whose components satisfy

$$\langle \eta_n^{\sigma}(\mathbf{x},t)\,\eta_m^{\sigma'}(\mathbf{y},t')\rangle = \delta_{n,m}\delta(t-t')\,\delta(\mathbf{x}-\mathbf{y})\,\delta_{\sigma,\sigma'}. \tag{4.15}$$

It can be checked that the Gaussian noises ξ_n and $\widehat{\xi}_n$ have the same correlation functions and are thus statistically identical. We thus obtain a system of DK equations for the global densities μ_n:

$$\frac{\partial \mu_n(\mathbf{x},t)}{\partial t} = \sqrt{2D}\boldsymbol{\nabla}\cdot\left[\sqrt{\mu_n(\mathbf{x},t)}\boldsymbol{\eta}_n(\mathbf{x},t)\right] + D\boldsymbol{\nabla}^2\mu_n(\mathbf{x},t) - \boldsymbol{\nabla}\cdot\left[\mu_n(\mathbf{x},t)\,\mathbf{A}_n(\mathbf{x})\right] \\ + \sum_{m=0}^{K-1} Q_{nm}\mu_m(\mathbf{x},t). \tag{4.16}$$

There are a number of significant differences between equation (4.16) and the corresponding DK equation (3.11) for a randomly switching environment. First, equation (4.16) involves an indexed set of global densities $\mu_n(\mathbf{x},t)$ rather than a single global density $\rho(\mathbf{x},t)$. Second, the only source of noise in equation (4.16) is the spatiotemporal Gaussian noise, whereas equation (3.11) also depends on the stochastic environmental state $N(t)$. The latter dependence explains why there are statistical correlations between non-interacting particles in the case of environmental switching but not intrinsic switching—equation (4.16) has already been averaged with respect to the intrinsic switching. Third, taking expectations of equation (4.16) with respect to the Gaussian noise and setting $u_n(\mathbf{x},t) = \langle \mu_n(\mathbf{x},t)\rangle$ yields a deterministic PDE rather than the hPDE (3.13):

$$\frac{\partial u_n(\mathbf{x},t)}{\partial t} = D\boldsymbol{\nabla}^2 u_n(\mathbf{x},t) - \boldsymbol{\nabla}\cdot\left[u_n(\mathbf{x},t)\,\mathbf{A}_n(\mathbf{x})\right] + \sum_{m=0}^{K-1} Q_{nm}u_m(\mathbf{x},t). \tag{4.17}$$

Equation (4.17) is identical in form to the CK equation (2.3) for a single actively switching process, whereas equation (4.16) is a stochastic version of the CK equation with density-dependent multiplicative noise.

4.2. Interacting Brownian particles and mean field theory

Further differences between environmental and particle switching arise when particle interactions are included. Let us return to the example of interacting overdamped Brownian particles considered in section 3.3, but now assume that each particle independently switches between different conformational states. Moreover, suppose that the pairwise interaction between the particles $(\mathbf{X}_j(t), N_j(t))$ and $(\mathbf{X}_k(t), N_k(t))$ is given by $-D\beta\boldsymbol{\nabla}K_{N_j(t)N_k(t)}(\mathbf{X}_j(t)-\mathbf{X}_k(t))$. That is, the interaction potential depends on the internal conformational states of the particle pair. (For simplicity, we assume that the effective external potential $V(\mathbf{x})$ seen by a particle is independent of its internal state.) The hybrid SDE of an individual particle takes the form

$$d\mathbf{X}_j(t) = -D\beta\left[\boldsymbol{\nabla}V(\mathbf{X}_j(t)) + \sum_{k=1}^{\mathcal{N}}\boldsymbol{\nabla}K_{N_j(t)N_k(t)}(\mathbf{X}_j(t)-\mathbf{X}_k(t))\right]dt + \sqrt{2D}d\mathbf{W}_j(t). \tag{4.18}$$

As before, we introduce the global densities (4.1) and follow the various steps used in the derivation of the density equation (4.8):

$$\begin{aligned}\frac{\partial\rho_i(\mathbf{x},n,t)}{\partial t} &= -\sqrt{2D}\boldsymbol{\nabla}\cdot[\rho_i(\mathbf{x},n,t)\boldsymbol{\xi}_i(t)] + D\boldsymbol{\nabla}^2\rho_i(\mathbf{x},n,t) + D\beta\boldsymbol{\nabla}\cdot\rho_i(\mathbf{x},n,t)\boldsymbol{\nabla}V(\mathbf{x})\\ &\quad + D\beta\mathbb{E}\left[\boldsymbol{\nabla}\cdot\widehat{\rho}_i(\mathbf{x},n,t)\int_{\mathbb{R}^d}\sum_{j=1}^{\mathcal{N}}\sum_{m=0}^{K-1}\widehat{\rho}_j(\mathbf{y},m,t)\boldsymbol{\nabla}K_{nm}(\mathbf{x}-\mathbf{y})d\mathbf{y}\right]\\ &\quad + \sum_{m=0}^{K-1}Q_{nm}\rho_i(\mathbf{x},m,t),\end{aligned} \tag{4.19}$$

where expectation is taken with respect to the discrete Markov process. Summing over the particle index i along identical lines to the non-interacting case then gives

$$\begin{aligned}\frac{\partial\mu_n(\mathbf{x},t)}{\partial t} &= \sqrt{2D}\boldsymbol{\nabla}\cdot\left[\sqrt{\mu_n(\mathbf{x},t)}\boldsymbol{\eta}_n(\mathbf{x},t)\right] + D\boldsymbol{\nabla}^2\mu_n(\mathbf{x},t) + \sum_m Q_{nm}\mu_m(\mathbf{x},t)\\ &\quad + D\beta\mathbb{E}\left[\boldsymbol{\nabla}\cdot\widehat{\mu}_n(\mathbf{x},t)\left(\boldsymbol{\nabla}V(\mathbf{x}) + \int_{\mathbb{R}^d}\sum_m\widehat{\mu}_m(\mathbf{y},t)\boldsymbol{\nabla}K_{nm}(\mathbf{x}-\mathbf{y})d\mathbf{y}\right)\right].\end{aligned} \tag{4.20}$$

In contrast to the non-interacting case, we no longer obtain a closed DK equation for $\mu_n(\mathbf{x},t)$ when taking expectations with respect to the discrete stochastic process. Consequently, averaging with respect to the white noise process yields a PDE for the one-particle density

$$u_n(\mathbf{x},t) = \langle\mu_n(\mathbf{x},t)\rangle = \left\langle\mathbb{E}\left[\sum_j\delta(\mathbf{x}-\mathbf{X}_j(t))\delta_{N_j(t),n}\right]\right\rangle, \tag{4.21}$$

which couples to the two-point correlation function

$$u_{nm}^{(2)}(\mathbf{x},\mathbf{y},t) = \left\langle\mathbb{E}\left[\sum_{j,k}\delta(\mathbf{x}-\mathbf{X}_j(t))\delta(\mathbf{y}-\mathbf{X}_k(t))\delta_{N_j(t),n}\delta_{N_k(t),m}\right]\right\rangle. \tag{4.22}$$

That is,

$$\frac{\partial u_n(\mathbf{x},t)}{\partial t} = D\boldsymbol{\nabla}^2 u_n(\mathbf{x},t) + \sum_m Q_{nm} u_m(\mathbf{x},t)$$
$$+ D\beta\left[\boldsymbol{\nabla}\cdot\left(u_n(\mathbf{x},t)\boldsymbol{\nabla}V(\mathbf{x}) + \int_{\mathbb{R}^d}\sum_m u^{(2)}_{nm}(\mathbf{x},\mathbf{y},t)\boldsymbol{\nabla}K_{nm}(\mathbf{x}-\mathbf{y})\,d\mathbf{y}\right)\right]. \tag{4.23}$$

This has a completely different structure compared to the corresponding hPDE for and interaction potential K_n that depends on the state of a randomly switching environment. In particular, replacing $A_n(\mathbf{x})$ and $\mathbf{F}(\mathbf{x}-\mathbf{y})$ in equation (3.30) by the terms $-D\beta\boldsymbol{\nabla}V(\mathbf{x})$ and $-D\beta\boldsymbol{\nabla}K_n(\mathbf{x}-\mathbf{y})$, respectively, we have

$$\frac{\partial u(\mathbf{x},t)}{\partial t} = D\boldsymbol{\nabla}^2 u(\mathbf{x},t) + \beta D\boldsymbol{\nabla}\cdot[u(\mathbf{x},t)\boldsymbol{\nabla}V(\mathbf{x})]$$
$$+\beta D\boldsymbol{\nabla}\cdot\int_{\mathbb{R}^d}\langle\rho(\mathbf{x},t)\rho(\mathbf{y},t)\rangle\boldsymbol{\nabla}K_n(\mathbf{x}-\mathbf{y})\,d\mathbf{y}. \tag{4.24}$$

One recent example of an active binary switching system of interacting particles involves a one-component soft colloidal system in which every particle can individually stochastically switch between two interaction states [30, 31]. The two states correspond to a 'small' ($n=0$) and 'big' ($n=1$) conformational state, respectively, such that the interaction potential is given by an indexed Gaussian:

$$K_{nm}(x) = a_{nm}\mathrm{e}^{-x^2/\sigma^2_{nm}}, \quad n,m = 0,1. \tag{4.25}$$

The discrete state $N(t)\in\{0,1\}$ evolves according to a two-state Markov chain with matrix generator

$$\mathbf{Q} = \begin{pmatrix} -\gamma & \alpha \\ \gamma & -\alpha \end{pmatrix}. \tag{4.26}$$

In [30, 31] it is assumed that the mean field limit holds in the case of weakly interacting switching particles, which then leads to a closed system of equations for $u_n(\mathbf{x},t)$:

$$\frac{\partial u_0(\mathbf{x},t)}{\partial t} = -\boldsymbol{\nabla}\cdot\mathbf{J}_0(\mathbf{x},t) - \gamma u_0(\mathbf{x},t) + \alpha u_1(\mathbf{x},t), \tag{4.27a}$$
$$\frac{\partial u_1(\mathbf{x},t)}{\partial t} = -\boldsymbol{\nabla}\cdot\mathbf{J}_1(\mathbf{x},t) + \gamma u_0(\mathbf{x},t) - \alpha u_1(\mathbf{x},t), \tag{4.27b}$$

where

$$\mathbf{J}_n(\mathbf{x},t) = -D\boldsymbol{\nabla}u_n(\mathbf{x},t) - \beta D u_n(\mathbf{x},t)\boldsymbol{\nabla}\left[V(\mathbf{x}) + \sum_{m=0}^{K-1}\int_{\mathbb{R}^d}K_{nm}(\mathbf{x}-\mathbf{y})u_m(\mathbf{y},t)\,d\mathbf{y}\right]. \tag{4.28}$$

Finally, as also shown by these authors, substituting equation (4.28) into the CK equations (4.27a) and (4.27b), and taking the fast switching limit yields a single equation for the scalar density $u(\mathbf{x},t) = \sigma_0 u_0(\mathbf{x},t) + \sigma_1 u_1(\mathbf{x},t)$, where $\sigma_0 = \alpha/(\alpha+\gamma)$ and $\sigma_1 = \gamma/(\alpha+\gamma)$:

$$\frac{\partial u(\mathbf{x},t)}{\partial t} = D\boldsymbol{\nabla}^2 u(\mathbf{x},t) + D\beta\boldsymbol{\nabla}\cdot u(\mathbf{x},t)\left(\boldsymbol{\nabla}V(\mathbf{x}) + \int_{\mathbb{R}^d} \boldsymbol{\nabla}\overline{K}(\mathbf{x}-\mathbf{y})\, u(\mathbf{y},t)\, d\mathbf{y}\right), \tag{4.29}$$

where

$$\overline{K}(\mathbf{x}-\mathbf{y}) = \sum_{n,m} \sigma_n \sigma_m K_{nm}(\mathbf{x}-\mathbf{y}). \tag{4.30}$$

5. Nonequilibrium statistical field theory (non-interacting particles)

The analysis of the stochastic global density equations derived in this paper is nontrivial even in the absence of pairwise interactions. In the case of a randomly switching environment, the density equation is given by the hybrid DK equation (3.11), whereas for particle switching it takes the form of the system of DK equation (4.16). One approach is to recast the density equations into a field theory. This provides a framework for performing perturbative series expansions and, in certain cases, yields non-perturbative approximations to various correlation functions. As a first step in this direction, a field theory for a non-interacting, non-switching Brownian gas has recently been constructed for the global density [65]. The basic idea is to apply a MSRJD path integral construction [66–68] to the DK equation obtained by setting $A_n(\mathbf{x}) = 0$ in equation (3.11). (For a complementary approach based on a Doi-Peliti path integral formulation [69–71], see [72]. Note, however, that care has to be taken when comparing Doi-Peliti and MSRJD field theories since the actual fields have different physical interpretations.) One of the interesting features of the MSRJD path integral representation is that, even though the particles do not interact, the resulting field theory contains an interaction term. The presence of a 3-vertex reflects the original particle nature of the gas, and ensures that the density field is strictly positive, in contrast to a Gaussian free field. In this final section, we indicate how to extend the MSRJD path integral to the more general DK equations obtained in previous sections for non-interacting particle systems.

5.1. MSRJD path integral: particle switching

In order to simplify our derivation, we consider a 1D model with two internal states $n = 0,1$. Equation (4.16) reduces to the form

$$\begin{aligned}\frac{\partial \mu_n(x,t)}{\partial t} &= \sqrt{2D}\partial_x\left[\sqrt{\mu_n(x,t)}\eta_n(x,t)\right] + D\partial_x^2\mu_n(x,t) - \partial_x\left[\mu_n(x,t)A_n(x)\right] \\ &\quad + \sum_{m=0,1} Q_{nm}\mu_m(x,t),\end{aligned} \tag{5.1}$$

with the matrix generator given by equation (4.26). The first step in the MSRJD procedure is to discretize equation (5.1) by dividing the time interval $[0,t]$ into M equal subintervals of size Δt and setting

$$\phi_\ell(x) = \mu_0(x,\ell\Delta t), \quad \psi_\ell(x) = \mu_1(x,\ell\Delta t). \tag{5.2}$$

with fixed initial densities $\phi_0(x)$ and $\psi_0(x)$. Equation (5.1) becomes

$$\phi_{\ell+1}(x) = \phi_\ell(x) + [\mathbb{L}_0\phi_\ell(x) + \alpha\psi_\ell(x) - \gamma\phi_\ell(x)]\Delta t + \sqrt{2D}\frac{d\sqrt{\phi_\ell(x)}\Delta W_{0,\ell}(x)}{dx}, \tag{5.3a}$$

$$\psi_{\ell+1}(x) = \psi_\ell(x) + [\mathbb{L}_1\psi_\ell(x) - \alpha\psi_\ell(x) + \gamma\phi_\ell(x)]\Delta t + \sqrt{2D}\frac{d\sqrt{\psi_\ell(x)}\Delta W_{1,\ell}(x)}{dx}, \tag{5.3b}$$

with $\ell = 0,\ldots,M-1$, and $\mathbb{L}_n$ are the linear operators

$$\mathbb{L}_n f(x) = -\frac{d[A_n(x)f(x)]}{dx} + D\frac{d^2f(x)}{dx^2}. \tag{5.4}$$

Moreover $\Delta W_{n,\ell}(x)$ is a Gaussian random variable with zero mean and two-point correlation

$$\langle \Delta W_{n,\ell}(x)\Delta W_{n',\ell'}(y)\rangle = \delta_{\ell,\ell'}\delta_{n,n'}\delta(x-y)\Delta t. \tag{5.5}$$

Consider a particular realization of the spatiotemporal Gaussian noise processes, which we represent by the symbol Ω. Defining the vectors $\Phi = (\phi_1,\ldots,\phi_M)$ and $\Psi = (\psi_1,\ldots,\psi_M)$, we introduce the conditional probability density functional

$$\begin{aligned}
&\mathcal{P}[\Phi,\Psi|\phi_0,\psi_0,\Omega] \\
&\quad = \prod_{\ell=0}^{M-1}\prod_x \delta\left(\phi_{\ell+1}(x) - \phi_\ell(x) - [\mathbb{L}_0\phi_\ell(x) + \alpha\psi_\ell(x) - \gamma\phi_\ell(x)]\Delta t - \sqrt{2D}\Delta\widehat{W}_{0,\ell}(x)\right) \\
&\qquad \times \prod_{\ell=0}^{M-1}\prod_x \delta\left(\psi_{\ell+1}(x) - \psi_\ell(x) - [\mathbb{L}_1\psi_\ell(x) - \alpha\psi_\ell(x) + \gamma\phi_\ell(x)]\Delta t - \sqrt{2D}\Delta\widehat{W}_{1,\ell}(x)\right).
\end{aligned} \tag{5.6}$$

We have used the compact notation

$$\Delta\widehat{W}_{0,\ell}(x) = \frac{d\sqrt{\phi_\ell(x)}\Delta W_{0,\ell}(x)}{dx}, \quad \Delta\widehat{W}_{1,\ell}(x) = \frac{d\sqrt{\psi_\ell(x)}\Delta W_{1,\ell}(x)}{dx}. \tag{5.7}$$

Introducing Fourier representations of the Dirac delta functions gives

$$\mathcal{P}[\Phi,\Psi|\phi_0,\psi_0,\Omega] = \int \mathcal{D}\left[\widetilde{\Phi},\widetilde{\Psi}\right] \tag{5.8}$$

$$\begin{aligned}
&\times \exp\left\{i\sum_{\ell=0}^{M-1}\int dx\,\widetilde{\phi}_{\ell+1}(x)\left[\phi_{\ell+1}(x) - \phi_\ell(x) - (\mathbb{L}_0\phi_\ell(x) + \alpha\psi_\ell(x) - \gamma\phi_\ell(x))\Delta t\right]\right\} \\
&\times \exp\left\{i\sum_{\ell=0}^{M-1}\int dx\,\widetilde{\psi}_{\ell+1}(x)\left[\psi_{\ell+1}(x) - \psi_\ell(x) - (\mathbb{L}_1\psi_\ell(x) - \alpha\psi_\ell(x) + \gamma\phi_\ell(x))\Delta t\right]\right\} \\
&\times \exp\left\{\sqrt{2D}\sum_{\ell=0}^{M-1}\int dx\left[\partial_x\left[i\widetilde{\phi}_\ell(x)\right]\sqrt{\phi_\ell(x)}\Delta W_{0,\ell}(x)\right.\right. \\
&\quad \left.\left. +\partial_x\left[i\widetilde{\psi}_{\ell+1}(x)\right]\sqrt{\psi_{\ell+1}(x)}\Delta W_{1,\ell}(x)\right]\right\},
\end{aligned} \tag{5.9}$$

where $\mathcal{D}[\widetilde{\Phi},\widetilde{\Psi}] = \prod_{\ell=0}^{M-1}\prod_x d\widetilde{\phi}_\ell(x)d\widetilde{\psi}_\ell(x)$. We have integrated by parts in the final exponential factor. The final steps are to integrate with respect to the Gaussian processes and then to take the continuum limit $\Delta t \to 0$ and $M \to \infty$ with $M\Delta t = t$ and $\widetilde{\phi}(x,\ell\Delta t) = \widetilde{\phi}_\ell(x)$ etc. After performing the Wick rotation $(\widetilde{\phi},\widetilde{\psi}) \to (i\widetilde{\phi}, i\widetilde{\psi})$ we obtain a formal path integral representation of the probability density functional

$$\mathcal{P}[\phi,\psi] = \int \mathcal{D}\left[\widetilde{\phi},\widetilde{\psi}\right]\exp\left(-S\left[\phi,\widetilde{\phi},\psi,\widetilde{\psi}\right]\right) \tag{5.10}$$

where

$$\begin{aligned}
S&\left[\phi,\widetilde{\phi},\psi,\widetilde{\psi}\right] \\
&= \int_0^t d\tau \int_{-\infty}^{\infty} dx \left\{\widetilde{\phi}(x,\tau)\left[\partial_\tau\phi(x,\tau) + \gamma\phi(x,\tau) + \partial_x\left[A_0(x)\phi(x,\tau)\right] - D\partial_{xx}\phi(x,\tau)\right]\right. \\
&\quad + \widetilde{\psi}(x,\tau)\left[\partial_\tau\psi(x,\tau) + \alpha\psi(x,\tau) + \partial_x\left[A_1(x)\psi(x,\tau)\right] - D\partial_{xx}\psi(x,\tau)\right] \\
&\quad - \left[\alpha\widetilde{\phi}(x,\tau)\psi(x,\tau) + \gamma\widetilde{\psi}(x,\tau)\phi(x,\tau)\right] - D\left[\phi(x,\tau)\left(\partial_x\widetilde{\phi}(x,\tau)\right)^2\right. \\
&\quad \left.\left. + \psi(x,\tau)\left(\partial_x\widetilde{\psi}(x,\tau)\right)^2\right]\right\} + S_{\mathrm{IC}}\left[\phi,\widetilde{\phi},\psi,\widetilde{\psi}\right].
\end{aligned} \tag{5.11}$$

We have incorporated the initial conditions into the path integral by adding the following terms to the action (5.11):

$$S_{IC} = \int_0^t d\tau \int_{-\infty}^{\infty} dx \left\{\widetilde{\phi}(x,\tau)\delta(\tau)\left[\phi(x,\tau) - \rho_0(x)\right] + \widetilde{\psi}(x,\tau)\delta(\tau)\left[\psi(x,\tau) - \rho_1(x)\right]\right\}. \tag{5.12}$$

5.2. Moment generating functional

One typically uses path integrals to calculate expectations of the various fields and their composites. In particular, important quantities such as two-point correlations can be obtained by taking functional derivatives of the moment generating functional

$$\begin{aligned}
Z&\left[\mathbf{h},\widetilde{\mathbf{h}}\right] \\
&= \int \mathcal{D}\left[\phi,\widetilde{\phi},\psi,\widetilde{\psi}\right]\exp\left(-S\left[\phi,\widetilde{\phi},\psi,\widetilde{\psi}\right] + \left\{\widetilde{\phi},h_0\right\} + \left\{\widetilde{\psi},h_1\right\} + \left\{\phi,\widetilde{h}_0\right\} + \left\{\psi,\widetilde{h}_1\right\}\right),
\end{aligned} \tag{5.13}$$

where $\mathbf{h} = (h_0,h_1)$, $\widetilde{\mathbf{h}} = (\widetilde{h}_0,\widetilde{h}_1)$ and

$$\{a,b\} := \int_0^t d\tau \int_{-\infty}^{\infty} dx\, a(x,\tau)\, b(x,\tau). \tag{5.14}$$

For example,

$$\langle\phi(x,t)\,\phi(y,t_0)\rangle = \frac{1}{Z}\left.\frac{\delta^2 Z\left[\mathbf{h},\widetilde{\mathbf{h}}\right]}{\delta\widetilde{h}_0(x,t)\,\delta\widetilde{h}_0(y,t_0)}\right|_{\mathbf{h}=0=\widetilde{\mathbf{h}}} \tag{5.15}$$

etc (Note that the normalization of the path integral measure cancels in the definition of expectations such as $\langle\phi(x,t)\phi(y,t_0)\rangle$.) Suppose that we decompose the action (5.11) according to

$$S\left[\phi,\widetilde{\phi},\psi,\widetilde{\psi}\right] = S_0\left[\phi,\widetilde{\phi},\psi,\widetilde{\psi}\right] - S_I\left[\phi,\widetilde{\phi},\psi,\widetilde{\psi}\right], \tag{5.16}$$

where

$$S_0\left[\phi,\widetilde{\phi},\psi,\widetilde{\psi}\right] = \left\{\widetilde{\phi},(\partial_\tau+\gamma-\mathbb{L}_0)\,\phi\right\} + \left\{\widetilde{\psi},(\partial_\tau+\alpha-\mathbb{L}_1)\,\psi\right\}, \tag{5.17}$$

with $\mathbb{L}_n$ given by equation (5.4), and

$$\begin{aligned} S_I\left[\phi,\widetilde{\phi},\psi,\widetilde{\psi}\right] = {} & \alpha\left\{\widetilde{\phi},\psi\right\} + \gamma\left\{\widetilde{\psi},\phi\right\} + D\left[\left\{\phi,\left(\partial_x\widetilde{\phi}\right)^2\right\} + \left\{\psi,\left(\partial_x\widetilde{\psi}\right)^2\right\}\right] \\ & - S_{\mathrm{IC}}\left[\phi,\widetilde{\phi},\psi,\widetilde{\psi}\right]. \end{aligned} \tag{5.18}$$

The generating functional (5.13) can then be rewritten as

$$Z\left[\mathbf{h},\widetilde{\mathbf{h}}\right] = \exp\left(S_I\left(\delta/\delta\widetilde{h}_0,\delta/\delta h_0,\delta/\delta\widetilde{h}_1,\delta/\delta h_1\right)\right)\, Z_0\left[h_0,\widetilde{h}_0\right] Z_1\left[h_1,\widetilde{h}_1\right], \tag{5.19}$$

where

$$Z_0\left[h_0,\widetilde{h}_0\right] = \int\mathcal{D}\left[\phi,\widetilde{\phi}\right]\exp\left(-\left\{\widetilde{\phi},(\partial_\tau+\gamma-\mathbb{L}_0)\,\phi\right\} + \left\{\widetilde{\phi},h_0\right\} + \left\{\phi,\widetilde{h}_0\right\}\right), \tag{5.20a}$$

$$Z_1\left[h_1,\widetilde{h}_1\right] = \int\mathcal{D}\left[\psi,\widetilde{\psi}\right]\exp\left(-\left\{\widetilde{\psi},(\partial_\tau+\alpha-\mathbb{L}_1)\,\psi\right\} + \left\{\widetilde{\psi},h_1\right\} + \left\{\psi,\widetilde{h}_1\right\}\right). \tag{5.20b}$$

We have used the standard field theoretic trick of taking the interacting part of the action outside the path integral by replacing each field by its dual functional operator. For example,

$$\left\{\widetilde{\phi},\psi\right\} \to \left\{\delta/\delta h_0,\delta/\delta\widetilde{h}_1\right\} = \int_0^t d\tau\int_{-\infty}^{\infty}dx\,\frac{\delta}{\delta h_0\,(x,\tau)}\,\frac{\delta}{\delta\widetilde{h}_1\,(x,\tau)}, \tag{5.21}$$

and

$$\begin{aligned} &\left\{\delta/\delta h_0,\delta/\delta\widetilde{h}_1\right\} Z_0\left[h_0,\widetilde{h}_0\right] Z_1\left[h_1,\widetilde{h}_1\right] = \int_0^t d\tau\int_{-\infty}^{\infty}dx\,\frac{\delta Z_0\left[h_0,\widetilde{h}_0\right]}{\delta h_0\,(x,\tau)}\,\frac{\delta Z_1\left[h_1,\widetilde{h}_1\right]}{\delta\widetilde{h}_1\,(x,\tau)} \\ &= \int_0^t d\tau\int_{-\infty}^{\infty}dx\left[\int\mathcal{D}\left[\phi,\widetilde{\phi}\right]\widetilde{\phi}\,(x,\tau)\,\mathrm{e}^{-\left\{\widetilde{\phi},(\partial_\tau+\gamma-\mathbb{L}_0)\phi\right\}+\left\{\widetilde{\phi},h_0\right\}+\left\{\phi,\widetilde{h}_0\right\}}\right] \\ &\quad\times\left[\int\mathcal{D}\left[\psi,\widetilde{\psi}\right]\psi\,(x,\tau)\,\mathrm{e}^{-\left\{\widetilde{\psi},(\partial_\tau+\alpha-\mathbb{L}_1)\psi\right\}+\left\{\widetilde{\psi},h_1\right\}+\left\{\psi,\widetilde{h}_1\right\}}\right]. \end{aligned} \tag{5.22}$$

Assuming that we can reverse the order of the functional and ordinary integrals, we have

$$\begin{aligned} &\left\{\delta/\delta h_0,\delta/\delta\widetilde{h}_1\right\} Z_0\left[h_0,\widetilde{h}_0\right] Z_1\left[h_1,\widetilde{h}_1\right] \\ &\quad= \int\mathcal{D}\left[\phi,\widetilde{\phi},\psi,\widetilde{\psi}\right]\left[\int_0^t d\tau\int_{-\infty}^{\infty}dx\,\widetilde{\phi}\,(x,\tau)\,\psi\,(x,\tau)\right] \\ &\qquad\times\exp\left(-S_0\left[\phi,\widetilde{\phi},\psi,\widetilde{\psi}\right] + \left\{\widetilde{\phi},h_0\right\} + \left\{\widetilde{\psi},h_1\right\} + \left\{\phi,\widetilde{h}_0\right\} + \left\{\psi,\widetilde{h}_1\right\}\right). \end{aligned} \tag{5.23}$$

It immediately follows that

$$
\begin{aligned}
&\mathrm{e}^{\alpha\left\{\delta/\delta h_0,\delta/\delta\widetilde{h}_1\right\}} Z_0\left[h_0,\widetilde{h}_0\right] Z_1\left[h_1,\widetilde{h}_1\right] \\
&\quad = \int \mathcal{D}\left[\phi,\widetilde{\phi},\psi,\widetilde{\psi}\right] \exp\left(\alpha\left\{\widetilde{\phi},\psi\right\}\right) \\
&\quad\quad \times \exp\left(-S_0\left[\phi,\widetilde{\phi},\psi,\widetilde{\psi}\right] + \left\{\widetilde{\phi},h_0\right\} + \left\{\widetilde{\psi},h_1\right\} + \left\{\phi,\widetilde{h}_0\right\} + \left\{\psi,\widetilde{h}_1\right\}\right).
\end{aligned} \tag{5.24}
$$

The other terms in the action S_I can be treated along analogous lines, and thus we establish the validity of equation (5.19).

Evaluating the Gaussian integrals (5.20a) and (5.20b) gives

$$
Z_n\left[h_n,\widetilde{h}_n\right] = \exp\left(\int d\tau d\tau' dx dx' \widetilde{h}_n(x,\tau)\, G_n(x,\tau|x',\tau')\, h_n(x',\tau')\right), \tag{5.25}
$$

where $G_n(x,t|x_0,t_0)$ are casual Green's functions. That is,

$$
G_0(x,t|x_0,t_0) = \mathrm{e}^{-\gamma(t-t_0)} p_0(x,t|x_0,t_0)\,\Theta(t-t_0), \tag{5.26a}
$$

$$
G_1(x,t|x_0,t_0) = \mathrm{e}^{-\alpha(t-t_0)} p_1(x,t|x_0,t_0)\,\Theta(t-t_0), \tag{5.26b}
$$

where $\Theta(t)$ is the Heaviside function, and $p_n(x,t|x_0,t_0)$ is the solution to the Fokker-Planck equation

$$
\frac{\partial p_n}{\partial t} = \mathbb{L}_n p_n \equiv -\frac{\partial\left[A_n(x)\,p_n\right]}{\partial x} + D\frac{\partial^2 p_n}{\partial x^2}, \tag{5.27}
$$

under the initial condition $p_n(x,t_0|x_0,t_0) = \delta(x-x_0)$. The exponential factors $\mathrm{e}^{-\gamma(t-t_0)}$ and $\mathrm{e}^{-\alpha(t-t_0)}$ appearing in equations (5.26a) and (5.26b) are the probabilities that there are no transitions $0\to 1$ and $1\to 0$, respectively, over the time interval $[t_0,t]$. One non-trivial example for which p_n can be calculated explicitly is an Ornstein–Uhlenbeck (OU) process with random drift. This particular hSDE has been used to model an RTP with diffusion in a harmonic potential [73, 74] and protein synthesis in a gene network [12, 13]. In the former case, $X(t)\in\mathbb{R}$ represents the position of the RTP at time t whereas $N(t)=n\in\{0,1\}$ specifies the current velocity state v_n of the particle. If $v_0=v$ and $v_1=-v$ then the motion becomes unbiased when the mean time spent in each velocity state is the same ($\alpha=\gamma$). On the other hand, in the case of the gene network, $X(t)$ represents the current concentration of synthesized protein and $N(t)$ specifies whether the gene is active or inactive. That is, v_n is the rate of synthesis with $v_0>v_1\geqslant 0$. In both examples, the variable $X(t)$ evolves according to the hSDE

$$
dX(t) = \left[-\kappa_0 X(t) + v_n\right]dt + \sqrt{2D}dW(t), \quad N(t)=n, \tag{5.28}
$$

where κ_0 represents an effective 'spring constant' for an RTP in a harmonic potential, whereas it corresponds to a protein degradation rate in the case of a gene network. Comparison with equation (2.1) implies that $A_n(x) = -\kappa_0 x + v_n$. One major difference between an RTP and a gene network is that the continuous variable $X(t)$ has to be positive in the latter case. However, one often assumes that the effective 'harmonic potential' for $v_0>v_1\geqslant 0$ restricts $X(t)$ to positive values with high probability so that the condition $X(t)\geqslant 0$ does not have to be imposed explicitly. (If $D=0$ then $X(t)\in\Sigma=[v_0/\kappa_0, v_1/\kappa_0]$ and the CK equation can be restricted to the finite interval Σ with reflecting boundary conditions at the ends. In this case, the steady-state CK equation can be solved explicitly [11–13].) In the case of an OU process with random drift, one finds that

$$p_n(x,t|x_0,0) = \frac{1}{\sqrt{2\pi\Sigma(t)}} \exp\left(-\frac{\left[x - x_0 \mathrm{e}^{-\kappa_0 t} - v_n\left(1-\mathrm{e}^{-\kappa_0 t}\right)/\kappa_0\right]^2}{2\Sigma(t)}\right), \tag{5.29}$$

with

$$\Sigma(t) = \frac{D}{\kappa_0}\left(1-\mathrm{e}^{-2\kappa_0 t}\right). \tag{5.30}$$

Equation (5.19) is the starting point for performing various diagrammatic expansions by Taylor expanding the functional operator e^{S_I}. This has been carried out elsewhere for a non-switching Brownian gas [65, 72] whose MSRJD action is of the form

$$S\left[\phi,\widetilde{\phi}\right] = \left\{\widetilde{\phi},\left(\partial_\tau - D\partial_x^2\right)\phi\right\} - D\left\{\phi,\left(\partial_x\widetilde{\phi}\right)^2\right\} + S_{\mathrm{IC}}\left[\phi,\widetilde{\phi}\right]. \tag{5.31}$$

The cubic term on the right-hand side generates 3-vertices in any diagrammatic expansion of the path integral, and these play a key role in ensuring positivity of the global density. On the other hand, suppose that we first average the global density equation (5.1) with respect to the spatiotemporal white noise. This yields a deterministic PDE for the first moments $u_n(x,t) = \langle\mu_n(x,t)\rangle$ given by the CK equation

$$\frac{\partial u_0}{\partial t} = \mathbb{L}_0 u_0(x,t) - \gamma u_0(x,t) + \alpha u_1(x,t), \tag{5.32a}$$

$$\frac{\partial u_1}{\partial t} = \mathbb{L}_1 u_1(x,t) + \gamma u_0(x,t) - \alpha u_1(x,t). \tag{5.32b}$$

Although this is a deterministic system, it is still possible to carry out the MSRJD construction to obtain the generating functional (5.13) with the action functional (5.16) such that $S_I = \alpha\{\widetilde{\phi},\psi\} + \gamma\{\widetilde{\psi},\phi\} - S_{\mathrm{IC}}$. An expansion of e^{S_I} now generates contributions involving a fixed number of switching events. (Note that a Doi–Peliti version of this path integral construction has recently been applied to the particular example of a single RTP with diffusion in a 1D harmonic potential [74]. Analogous path integrals have also been developed for RTPs in higher dimensions [75] and active OU particles [76].)

5.3. MSRJD path integral: environmental switching

Developing a corresponding MSRJD field theory for environmental switching is more involved. For the sake of illustration, consider a 1D, 2-state version of the hybrid DK equation (3.11). As a further simplification, we average with respect to the white noise to obtain the hPDE

$$\frac{\partial u(x,t)}{\partial t} = D\frac{\partial^2 u(x,t)}{\partial x^2} - \frac{\partial\left[u(x,t)A_{N(t)}(x)\right]}{\partial x}, \tag{5.33}$$

where $N(t)$ switches according to a 2-state Markov chain with matrix generator (4.26). Following along analogous lines to the construction of section 5.1, we discretize equation (5.33) by dividing the time interval $[0,t]$ into M equal subintervals of size Δt

and setting $u_\ell(x) = u(x, \ell\Delta t)$ with a fixed initial density $u_0(x)$ that is twice differentiable. Equation (5.33) becomes

$$u_{\ell+1}(x) = u_\ell(x) + \mathbb{L}_n u_\ell(x)\Delta t, \quad N(t) = n \tag{5.34}$$

with $\ell = 0, \ldots, M-1$, and $\mathbb{L}_n$ defined in equation (5.4). Consider a particular realization of the discrete stochastic process $N(\ell\Delta t) = n_\ell$ and set $\mathbf{n} = (n_0, \ldots, n_{M-1})$. Defining $U = (u_1, \ldots, u_M)$, we introduce the conditional probability density functional

$$\mathcal{P}[U|u_0, \mathbf{n}] = \prod_{\ell=0}^{M-1}\prod_x \delta\left(u_{\ell+1}(x) - u_\ell(x) - \mathbb{L}_{n_\ell}u_\ell(x)\Delta t\right). \tag{5.35}$$

Inserting the Fourier representation of the Dirac delta function gives

$$\mathcal{P}[U|u_0, \mathbf{n}] = \int \mathcal{D}\left[\widetilde{U}\right]\exp\left\{i\sum_{\ell=0}^{M-1}\int dx\widetilde{u}_{\ell+1}(x)\left[u_{\ell+1}(x) - u_\ell(x) - \mathbb{L}_{n_\ell}u_\ell(x)\Delta t\right]\right\}. \tag{5.36}$$

If we now average over the intermediate discrete states $n_\ell, \ell = 1, M-1$ then

$$\mathcal{P}[U, n_M|u_0, n_0] = \int \mathcal{D}[\widetilde{U}]\exp\left\{i\sum_{\ell=0}^{M-1}\int dx\widetilde{u}_{\ell+1}(x)\left[u_{\ell+1}(x) - u_\ell(x)\right]\right\}$$
$$\times \left[\mathrm{e}^{[\mathbf{Q}+\mathbf{K}[\widetilde{u}_M, u_{M-1}]\Delta t}\cdots\mathrm{e}^{[\mathbf{Q}+\mathbf{K}[\widetilde{u}_1, u_0]\Delta t]}\right]_{n_M n_0}, \tag{5.37}$$

where $\mathbf{Q}$ is the matrix generator of the Markov process, n_M and n_0 are the initial and final discrete states, and

$$\mathbf{K}[\widetilde{u}_{\ell+1}, u_\ell] = \begin{pmatrix} -i\int dx\widetilde{u}_{\ell+1}(x)\mathbb{L}_0 u_\ell(x) & 0 \\ 0 & -i\int dx\widetilde{u}_{\ell+1}(x)\mathbb{L}_1 u_\ell(x)\end{pmatrix}. \tag{5.38}$$

In order to obtain a meaningful action functional in the continuum limit, it is necessary to diagonalize the matrix products on the second line of equation (5.37). One method is to use coherent spin states along analogous lines to the study of hSDEs for gene networks [77–80]. This requires the introduction of auxiliary variables for the path integral action. For a two-state hybrid systems, we first decompose the matrix $\mathbf{H} = \mathbf{K} + \mathbf{Q}$ using the Pauli spin matrices

$$\sigma_x = \frac{1}{2}\begin{pmatrix} 0 & 1 \\ 1 & 0\end{pmatrix}, \quad \sigma_y = \frac{1}{2}\begin{pmatrix} 0 & -i \\ i & 0\end{pmatrix}, \quad \sigma_z = \frac{1}{2}\begin{pmatrix} 1 & 0 \\ 0 & -1\end{pmatrix}. \tag{5.39}$$

That is

$$\mathbf{H} = \left(\frac{1}{2}\mathbf{1} + \sigma_z\right)K_0 + \left(\frac{1}{2}\mathbf{1} - \sigma_z\right)K_1 - \gamma\left(\frac{1}{2}\mathbf{1} + \sigma_z\right) - \alpha\left(\frac{1}{2}\mathbf{1} - \sigma_z\right) + \alpha\sigma_+ + \gamma\sigma_-,$$

where $\sigma_\pm = \sigma_x \pm i\sigma_y$ and $K_n[\widetilde{u}, u] = -i\int dx\widetilde{u}(x)\mathbb{L}_n u(x)$. Next we define the coherent spin-1/2 state [81]

$$|s\rangle = \begin{pmatrix} \mathrm{e}^{i\phi/2}\cos^2\theta/2 \\ \mathrm{e}^{-i\phi/2}\sin^2\theta/2\end{pmatrix}, \quad 0 \leqslant \theta \leqslant \pi,\ 0 \leqslant \phi < 2\pi, \tag{5.40}$$

together with the adjoint

$$\langle s| = \left(\mathrm{e}^{-i\phi/2}, \mathrm{e}^{i\phi/2}\right). \tag{5.41}$$

Note that

$$\langle s'|s\rangle = \mathrm{e}^{i\left(\phi-\phi'\right)/2}\cos^2\theta/2 + \mathrm{e}^{-i\left(\phi-\phi'\right)/2}\sin^2\theta/2, \tag{5.42}$$

so that $\langle s|s\rangle = 1$ and

$$\langle s+\Delta s|s\rangle = 1 - \frac{1}{2}i\Delta\phi\cos\theta + O\left(\Delta\phi^2\right). \tag{5.43}$$

We also have the completeness relation

$$\frac{1}{2\pi}\int_0^{\pi}\sin\theta\, d\theta\int_0^{2\pi}d\phi\, |s\rangle\langle s| = 1. \tag{5.44}$$

It can checked that the following identities hold:

$$\langle s|\sigma_z|s\rangle = \frac{1}{2}\cos\theta,\ \langle s|\sigma_+|s\rangle = \frac{1}{2}\mathrm{e}^{i\phi}\sin\theta,\ \langle s|\sigma_-|s\rangle = \frac{1}{2}\mathrm{e}^{-i\phi}\sin\theta. \tag{5.45}$$

Hence,

$$\begin{aligned}\langle s|\mathbf{H}|s\rangle &= H[\theta,\phi,u,\widetilde{u}]\\ &\equiv -\left(\gamma\left[1-\mathrm{e}^{i\phi}\right] - K_0\left[\widetilde{u},u\right]\right)\frac{1+\cos\theta}{2} - \left(\alpha\left[1-\mathrm{e}^{-i\phi}\right] - K_1\left[\widetilde{u},u\right]\right)\frac{1-\cos\theta}{2}.\end{aligned} \tag{5.46}$$

We can now diagonalize the matrix product on the second line of equation (5.37) by inserting multiple copies of the completeness relations (5.44). Introducing the solid angle integral

$$\int_\Omega ds = \frac{1}{2\pi}\int_0^{\pi}\sin\theta\, d\theta\int_0^{2\pi}d\phi, \tag{5.47}$$

we have

$$\begin{aligned}&\int_\Omega ds_0\cdots\int_\Omega ds_M|s_M\rangle\langle s_M|\mathrm{e}^{\mathbf{H}[\widetilde{u}_M,u_{M-1}]\Delta t}|s_{N-1}\rangle\langle s_{N-1}|\mathrm{e}^{\mathbf{H}[\widetilde{u}_{M-1},u_{M-2}]\Delta t}|s_{N-2}\rangle\\ &\quad\cdots\times\langle s_1|\mathrm{e}^{\mathbf{H}[\widetilde{u}_1,u_0]\Delta t}|s_0\rangle\langle s_0|\psi(0)\rangle.\end{aligned} \tag{5.48}$$

In the limit $M\to\infty$ and $\Delta t\to 0$ with $M\Delta t = t$ fixed, we can make the approximation

$$\langle s_{\ell+1}|\mathrm{e}^{\mathbf{H}\Delta t}|s_\ell\rangle = \langle s_{\ell+1}|s_\ell\rangle\left\{1 + H[\theta_\ell,\phi_\ell,u_\ell,\widetilde{u}_{\ell+1}]\Delta t\right\} + O\left(\Delta t^2\right), \tag{5.49}$$

with H defined in equation (5.46). In addition, equation (5.43) and the restriction to continuous paths in the continuum limit implies that

$$\langle s_{\ell+1}|s_\ell\rangle = 1 - \frac{1}{2}i\left(\phi_{\ell+1}-\phi_\ell\right)\cos\theta_\ell + O\left(\Delta\phi^2\right) = 1 - \frac{1}{2}i\Delta t\frac{d\phi_\ell}{dt}\cos\theta_\ell + O\left(\Delta t^2\right). \tag{5.50}$$

Hence,

$$\langle s_{\ell+1}|\mathrm{e}^{\mathbf{H}\Delta t}|s_\ell\rangle \approx \exp\left(\left[H[\theta_\ell,\phi_\ell,u_\ell,\widetilde{u}_{\ell+1}] - \frac{i}{2}\frac{d\phi_\ell}{dt}\cos\theta_\ell\right]\Delta t\right). \tag{5.51}$$

We can now take the continuum limit. After Wick ordering, integrating by parts the term involving $d\phi/dt$, and performing the change of coordinates $z=(1+\cos\theta)/2$, we obtain the following functional path integral:

$$\mathcal{P}_{nn_0}[u] = \int \mathcal{D}[\theta]\mathcal{D}[z]\mathcal{D}[\widetilde{u}]\exp(-S[u,\widetilde{u},z,\theta]) \tag{5.52}$$

where

$$\begin{aligned} S[u,\widetilde{u},z,\theta] = \int_0^t d\tau \Bigg\{ &\int_{-\infty}^{\infty} dx \widetilde{u}(x,\tau)\partial_\tau u(x,\tau) - i\phi\frac{dz}{d\tau} \\ &+ z(\tau)\left[-\gamma\left(1-\mathrm{e}^{i\phi(\tau)}\right) + \int dx\widetilde{u}(x,\tau)\mathbb{L}_0 u(x,\tau)\right] \\ &+ (1-z(\tau))\left[-\alpha\left(1-\mathrm{e}^{-i\phi(\tau)}\right) + \int dx\widetilde{u}(x,\tau)\mathbb{L}_1 u(x,\tau)\right]\Bigg\}. \end{aligned} \tag{5.53}$$

6. Discussion

In this paper we derived global density equations for a population of actively switching particles by generalizing the classical formulation of Dean [32]. In the case of a randomly switching environment (extrinsic switching), we showed that the global density $\rho(\mathbf{x},t) = \sum_j \delta(\mathbf{X}_j(t)-\mathbf{x})$ evolves according to a hybrid DK equation. Averaging with respect to the spatiotemporal white noise process (and using mean-field theory or DDFT in the case of pairwise interactions), resulted in a hybrid PDE for the 1-particle density $u(\mathbf{x},t) = \langle\rho(\mathbf{x},t)\rangle$. We then derived moment equations from the corresponding functional CK equation (3.20), and used this to highlight how statistical correlations are induced by the randomly switching environment, even in the absence of particle-particle interactions. Such correlations are absent when the individual particles independently switch (intrinsic switching). In the latter case we derived a system of DK equations for the indexed set of global densities $\mu_n(\mathbf{x},t) = \sum_j \delta(\mathbf{X}_j(t)-\mathbf{x})\mathbb{E}[\delta_{N_j(t)=n}]$. However, the inclusion of particle interactions resulted in a moment closure problem for the global densities with respect to the switching process. Finally, we constructed MSRJD field theoretic formulations of the global density equations in the case of non-interacting particles.

For simplicity, we took the matrix generator $\mathbf{Q}$ of the switching process to be independent of the continuous process $\mathbf{X}(t)$, whereas many of the applications in cell biology involve state-dependent switching. For example, in the case of membrane voltage fluctuations, the opening and closing of the ion channels depends on the membrane voltage. Another important example is a gene network with regulatory feedback [11]. The simplest type of a feedback circuit involves a gene that is regulated by its own protein product (auroregulation), as shown in figure 4. Suppose that the promoter has a single operator site OS_1 for binding protein X. The gene is assumed to be OFF when X is bound to the promoter and ON otherwise. If O_0 and O_1 denote the unbound and bound promoter states, then the corresponding reaction scheme is

$$O_0 \underset{\alpha}{\overset{\beta x}{\rightleftharpoons}} O_1,$$

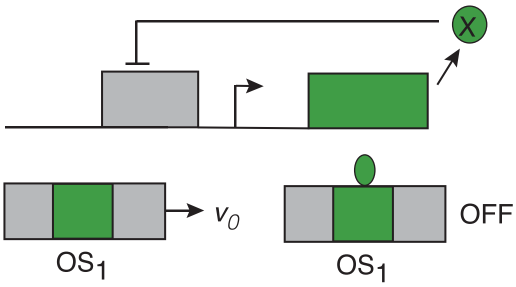

Figure 4. An autoregulatory gene network with single operator site OS_1. A gene is repressed (or activated) by its own protein product X.

where x is the concentration of X. The concentration evolves according to the piecewise deterministic equation

$$\frac{dx}{dt} = A_n(x), \quad \text{for } N(t) = n, \tag{6.1}$$

where $A_0(x) = \gamma_0 - \kappa_0 x$, $A_1(x) = -\kappa_0 x$ and discrete state transitions are generated by the matrix

$$\mathbf{Q}(x) = \begin{pmatrix} -\gamma x & \alpha \\ \gamma x & -\alpha \end{pmatrix}. \tag{6.2}$$

A third example involves switching diffusivities. Advances in single-particle tracking (SPT) and statistical methods suggest that particles within the plasma membrane, for example, switch between different discrete conformational states with different diffusivities [27–29]. Such switching could be due to interactions between proteins and the actin cytoskeleton or due to protein-lipid interactions. Interestingly, the switching rates between the different conformational states can also depend on the spatial location of a particle. For example, an experimental and computational study of *C. elegans* zygotes showed that protein concentration formation during cell polarization relies on a space-dependent switching mechanism [82]. This was independently predicted in a general theoretical study of protein gradient formation in switching systems [83, 84]. Note that state-dependent switching and switching diffusivities can be incorporated into the system of DK equation (4.16) as follows:

$$\begin{aligned}\frac{\partial \mu_n(\mathbf{x},t)}{\partial t} &= \sqrt{2D_n}\boldsymbol{\nabla}\cdot\left[\sqrt{\mu_n(\mathbf{x},t)}\boldsymbol{\eta}_n(\mathbf{x},t)\right] + D_n\boldsymbol{\nabla}^2\mu_n(\mathbf{x},t) - \boldsymbol{\nabla}\cdot\left[\mu_n(\mathbf{x},t)\mathbf{A}_n(\mathbf{x})\right] \\ &\quad + \sum_{m=0}^{K-1} Q_{nm}(\mathbf{x})\rho_m(\mathbf{x},t).\end{aligned} \tag{6.3}$$

Finally, in this paper we focused on the derivation and general mathematical structure of global density equations for actively switching systems, highlighting the differences between environmental and intrinsic switching. At least two theoretical issues are worth exploring when considering specific applications.

(A) *DDFT and meean field theory for actively switching particles.* There has been significant progress in the rigorous mathematical analysis of mean-field limits and McKean–Vlasov equations for weakly-interacting particle systems without switching [59–62]. An extension to a randomly switching environment has also been developed [64]. However, as far as we are aware, analogous results for the mean-field limit in the case of intrinsically switching particles has not been considered. As we showed in section 4.2, the inclusion of particle interactions leads to a moment closure problem at the level of the generalized DK equation for the global densities μ_n, see for example equation (4.20). The effects of environmental switching on the validity of the adiabatic approximation for DDFT also needs to be investigated. As highlighted in section 3.3, in the fast switching limit one could average with respect to switching and then apply DDFT, and vice versa in the slow switching limit. The difficulty arises at switching rates comparable to the rate of relaxation to thermodynamic equilibrium.

(B) *Weak noise limit.* One important application of statistical field theory is to the derivation of least action principles in the weak noise limit. For the given population model, there are two distinct sources of noise at the single particle level: (i) the stochastic switching between different internal states; (ii) external white noise with diffusivity D. The weak noise limit involves taking $D \to 0$ and $Q_{nm} \to \infty$. A typical feature of a stochastic path integral is that the sum-over-paths has support over the set of paths that are continuous but non-differentiable with respect to τ. In particular, any time derivative in the action functional is a formal symbol for the appropriate difference term in the time-discretized path integral. Nevertheless, in the weak noise limit, the path integral is dominated by paths that are arbitrarily close to the classical least action paths, which are differentiable.

Data availability statement

No new data were created or analysed in this study.

ORCID iD

Paul C Bressloff https://orcid.org/0000-0002-7714-9853

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