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Diffusive transport in the presence of stochastically gated absorption

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We analyze a population of Brownian particles moving in a spatially uniform environment with stochastically gated absorption. The state of the environment at time t is represented by a discrete stochastic variable $k(t) \in \{0,1\}$ such that the rate of absorption is $\gamma[1-k(t)]$, with γ a positive constant. The variable $k(t)$ evolves according to a two-state Markov chain. We focus on how stochastic gating affects the attenuation of particle absorption with distance from a localized source in a one-dimensional domain. In the static case (no gating), the steady-state attenuation is given by an exponential with length constant $\sqrt{D/\gamma}$, where D is the diffusivity. We show that gating leads to slower, nonexponential attenuation. We also explore statistical correlations between particles due to the fact that they all diffuse in the same switching environment. Such correlations can be determined in terms of moments of the solution to a corresponding stochastic Fokker-Planck equation.

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I. INTRODUCTION

A fundamental property of a one-dimensional diffusion-absorption process is that it generates an exponentially decaying steady-state solution in response to a localized source of particles. "Absorption" could be due to the presence of spatially distributed traps within or on the boundary of the medium [1–8] or due to degradation and/or inactivation of the diffusing particles as in the formation of protein gradients at the intracellular [9–12] and multicellular levels [13–17]. In the latter case, the presence of attenuation in the particle concentration plays a crucial role in cell signaling either coupling cell growth to the cell cycle or regulating gene activity according to spatial location during embryogenesis. On the other hand, attenuation can be a problem for diffusion-based forms of intracellular transport that distribute newly synthesized proteins to different regions of a cell. This issue is particularly acute for neurons, with their extensively branched dendrites that receive information from other neurons and a single long axon that delivers information over long distances to other neurons or muscle cells [18–21]. The presence of active motor-driven transport does not necessarily solve this problem, since the stochastic nature of molecular motor trafficking results in an effective advection-diffusion equation, which still results in attenuated steady-state concentrations of particles [22].

Recently, we have shown how attenuation of the steady-state concentration can be mitigated by taking the absorption of particles to be reversible [22–25]. Although our mathematical analysis was motivated by experimental studies of intracellular transport in neurons [26,27], it reflects a general feature of diffusion-absorption processes: If absorption of particles is reversible, then the particles absorbed close to the source are free to be re-released into the diffusing pool of particles for absorption at more distal regions. In this paper, we investigate another potential mechanism for mitigating attenuation, which is based on stochastic gating. The latter has been studied extensively within the context of diffusion-trapping problems [28–33] but, as far as we are aware, has not been considered within the context of the spatial distribution of diffusing molecules within cells. One of the important distinctions that has to be made in the case of stochastically gated diffusion is whether each diffusing particle is independently gated or the medium itself is gated. In the latter case, statistical correlations arise between the particles even when they are noninteracting, due to the fact that they move in the same fluctuating environment. We have explored this issue in a series of papers concerning diffusion in domains with stochastically gated exterior boundaries or interior barriers (gap junctions) [34–39]. In this paper we extend our analysis to the case of a population of Brownian particles moving in an environment with stochastically gated absorption. That is, the state of the environment at time t is represented by a discrete stochastic variable $k(t) \in \{0,1\}$ such that the rate of absorption is $\gamma[1-k(t)]$, with γ a positive constant. The variable $k(t)$ evolves according to a two-state Markov chain. For simplicity, we typically assume that the absorption process is spatially uniform, though we also consider an example of spatially heterogeneous absorption in Sec. V.

The structure of the paper is as follows. In Sec. II, we consider a single Brownian particle diffusing along the semi-infinite line $x \in [0,\infty)$, with a reflecting boundary at $x=0$. Assuming that the particle starts at $x=0$, we determine the steady-state absorption density $q(x)$ as a function of position x. In the case of a static absorption rate γ, we find that $q(x)$ decays exponentially with length constant $\sqrt{D/\gamma}$, where D is the diffusivity. On the other hand, if the absorption rate is stochastically gated, then the attenuation of $q(x)$ as a function of x is nonexponential and significantly slower. In Sec. III we turn to a large population of noninteracting Brownian particles diffusing in the same randomly switching environment. Given a particular realization of the environment, the population density evolves according to a Fokker-Planck (FP) equation with a time-dependent absorption rate. It follows that different realizations of the environment generate an ensemble of FP equations. We show how moments of the corresponding population densities, obtained by taking expectations with respect to realizations of the environment, evolve according to a hierarchy of differential Chapman-Kolmogorov (CK) equations. Analyzing the second-order moment equations allows us to determine the variance in the stochastic absorption density. In Sec. IV we develop an alternative approach to studying stochastically gated absorption by decomposing the solution into the product of a deterministic factor and a nonspatial stochastic factor. The latter is then analyzed using a method originally due to Kubo [40]. Finally, in Sec. V we consider an example of spatially heterogeneous, gated absorption involving N spatially localized traps. For simplicity, we assume that the stochastic gating of the traps is synchronized so that there is still a single gating variable $k(t) \in \{0,1\}$. If each trap had its own independent gate with discrete state $k_n(t) \in \{0,1\}$, then switching would be described by a Markov chain with 2^N states. Synchronized switching might occur if there were some form of coupling between the traps or some external drive that switches the traps.

II. SINGLE BROWNIAN PARTICLE WITH STOCHASTICALLY GATED ABSORPTION

A. Static absorption

Consider a single Brownian particle diffusing along the semi-infinite line $x \in [0,\infty)$. Suppose that at any point x the particle can be absorbed at a rate γ. (Such absorption could be due to a set of closely spaced discrete traps, as previously investigated within the context of diffusive transport in spiny dendrites of neurons [20].) Let $p(x,t)$ be the probability density for the particle to be at x at time t and not yet absorbed. Then

$$\frac{\partial p}{\partial t} = D\frac{\partial^2 p}{\partial x^2} - \gamma p. \tag{2.1}$$

We assume that the particle is initially injected at the end $x = 0$ and this boundary is reflecting. (Throughout this paper we fix the units of space and time by setting $D = 1$ and $\gamma = 0.1$.) Thus,

$$\left.\frac{\partial p(x,t)}{\partial x}\right|_{x=0} = 0; \quad p(x,0) = \delta(x). \tag{2.2}$$

Clearly in the large-time limit we have

$$\lim_{t\to\infty} p(x,t) = 0$$

for all $x \in \mathbb{R}^+$ so that there does not exist a nontrivial steady-state solution. One way to obtain a nontrivial steady-state solution is to consider a population of independent Brownian particles injected at the end $x = 0$ according to a constant flux J_0 and determine the resulting steady-state particle concentration $u(x)$. The latter takes the form of a decaying exponential

$$u(x) = \frac{J_0}{\sqrt{\gamma D}} e^{-\sqrt{\gamma/D}x}.$$

However, it is also possible to extract the exponential nature of the transport process at the level of a single Brownian particle.

The basic idea is to keep track of the probability flux into targets by introducing the density $q(x,t)$ such that

$$\frac{\partial q(x,t)}{\partial t} = \gamma p(x,t); \quad q(x,0) = 0. \tag{2.3}$$

Integrating with respect to times gives

$$q(x,t) = \gamma \int_0^t p(x,\tau)d\tau. \tag{2.4}$$

Although $p(x,t) \to 0$ as $t \to \infty$, one finds that

$$q(x,t) \to q(x) = \gamma \int_0^\infty p(x,\tau)d\tau \text{ as } t \to \infty. \tag{2.5}$$

Moreover, integrating Eq. (2.1) with respect to x and t and using Eqs. (2.2) establishes that $\int_0^\infty q(x)dx = 1$. In other words, $q(x)$ is the probability density that the particle is absorbed at x. It is straightforward to determine $q(x)$ using Laplace transforms. Setting

$$\widetilde{p}(x,s) = \int_0^\infty e^{-st} p(x,t)dt, \tag{2.6}$$

we see that $q(x) = \gamma \lim_{s\to 0} \widetilde{p}(x,s)$. Laplace transforming Eq. (2.1) and using the initial condition in (2.2) implies that for each s

$$D\frac{d^2\widetilde{p}}{dx^2} - (\gamma + s)\widetilde{p} = -\delta(x), \quad x \in (0,\infty); \quad \left.\frac{d\widetilde{p}}{dx}\right|_{x=0} = 0. \tag{2.7}$$

It follows that $\widetilde{p}(x,s)$ is determined by the Neumann Green's function on the semi-infinite line:

$$\widetilde{p}(x,s) = \frac{1}{\sqrt{(\gamma + s)D}} e^{-\sqrt{(\gamma+s)/D}x}. \tag{2.8}$$

We thus deduce that the probability density for absorption is an exponentially decaying function of x,

$$q(x) = \sqrt{\frac{\gamma}{D}} e^{-\sqrt{\gamma/D}x}. \tag{2.9}$$

Note that the expression for $q(x)$ can also be obtained directly from Eq. (2.12) by solving Eqs. (2.1) and (2.2) in the time domain. One finds that the solution is given by $[p(x,t) = \frac{1}{\sqrt{\pi Dt}} e^{-x^2/4Dt-\gamma t}]$. Substituting into Eq. (2.12), taking the limit $t \to \infty$ and evaluating the resulting integral recovers Eq. (2.9).

B. Gated absorption

Following previous work on diffusion in randomly switching environments [24,37], there are two alternative ways to introduce gated absorption; see Fig. 1. First, the Brownian particle can switch between two conformational states labeled $k = 0,1$, and is absorbed (degraded) only if it is in state $k = 0$. Alternatively, there exists a physical gate that can switch between two discrete states $k = 0,1$, so that the Brownian particle is absorbed only if the gate is in state $k = 0$. In the case of a single Brownian particle, these two scenarios are statistically equivalent. However, this equivalence breaks down in the case of a population of noninteracting Brownian particles moving in the same switching environment (see Sec. III).

We will assume that the discrete state $k(t) \in \{0,1\}$ evolves according to a two-state Markov chain with constant transition rates α,β. Let $X(t)$ denote the current position of the particle given that it has not yet been absorbed, and consider the Markov process $(X(t),k(t))$ with probability density

$$\begin{aligned} p_k(x,t)dx = \mathbb{P}[x \leqslant X(t) \leqslant x + dx, k(t) \\ = k|X(0) = 0, k(0) = 0]. \end{aligned} \tag{2.10}$$

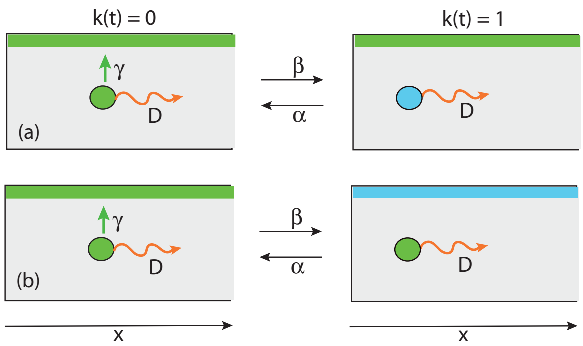

FIG. 1. Schematic diagram of a Brownian particle diffusing in a one-dimensional domain with gated absorption. Absorption can occur only when both the particle and the gate have the same color. (a) The particle switches between two conformational states, $k = 0,1$, and can be absorbed only in the state $k = 0$. The rate of absorption is γ, and the switching rates between the two conformational states are given by α,β. (b) Same as (a) except that now the gate, rather than the particle, switches state. (Note that in the figures diffusion is one-dimensional; the vertical coordinate is simply introduced to illustrate absorption.)

The probability densities $p_k(x,t)$, $k = 0,1$, evolve according to the differential CK equation

$$\frac{\partial p_0}{\partial t} = D\frac{\partial^2 p_0}{\partial x^2} - \gamma p_0 - \beta p_0 + \alpha p_1, \tag{2.11a}$$

$$\frac{\partial p_1}{\partial t} = D\frac{\partial^2 p_1}{\partial x^2} + \beta p_0 - \alpha p_1. \tag{2.11b}$$

These are supplemented by the initial conditions

$$p_k(x,0) = \rho_k \delta(x), \tag{2.11c}$$

with $\rho_0 + \rho_1 = 1$, and boundary conditions

$$\left.\frac{\partial p_k(x,t)}{\partial x}\right|_{x=0} = 0, \quad k = 0,1. \tag{2.11d}$$

Note that we could also take the diffusion coefficient to differ in the two states, but for simplicity we take them to be the same. Finally, we introduce the absorption density

$$q(x,t) = \gamma \int_0^t p_0(x,\tau)d\tau. \tag{2.12}$$

Again we use Laplace transforms to determine $q(x)$. Laplace transforming Eqs. (2.11a) and (2.11b) and using the initial conditions yields

$$D\frac{d^2\widetilde{p}_0}{dx^2} - (\gamma + \beta + s)\widetilde{p}_0 + \alpha\widetilde{p}_1 = -\rho_0\delta(x), \tag{2.13a}$$

$$D\frac{d^2\widetilde{p}_1}{dx^2} - (\alpha + s)\widetilde{p}_1 + \beta\widetilde{p}_0 = -\rho_1\delta(x), \tag{2.13b}$$

for $x \in (0,\infty)$. It is useful to rewrite these equations in matrix form by setting $\widetilde{\mathbf{p}} = (\widetilde{p}_0,\widetilde{p}_1)^\top$, with

$$D\frac{d^2\widetilde{\mathbf{p}}}{dx^2} - [\mathbf{A}(\gamma) + s\mathbf{I}]\widetilde{\mathbf{p}} = -\delta(x)\mathbf{e}_0, \quad x \in (0,\infty),$$

where

$$\mathbf{A}(\gamma) = \begin{pmatrix} \gamma + \beta & -\alpha \\ -\beta & \alpha \end{pmatrix}, \quad \mathbf{e}_0 = \begin{pmatrix} \rho_0 \\ \rho_1 \end{pmatrix}. \tag{2.14}$$

(We keep track of the dependence on γ because in Sec. IV we encounter similar equations except that $\gamma \to 2\gamma$.) Let us now set $s = 0$. Let $\lambda_\pm(\gamma)$ denote the eigenvalues of $\mathbf{A}(\gamma)$ with corresponding left and right eigenvectors denoted by $\widehat{\mathbf{v}}_\pm(\gamma)$ and $\mathbf{v}_\pm(\gamma)$, respectively, with $\widehat{\mathbf{v}}_\pm \cdot \mathbf{v}_\mp = 0$. Note in particular that

$$\lambda_\pm(\gamma) = \tfrac{1}{2}[\alpha + \beta + \gamma \pm \sqrt{(\alpha + \beta + \gamma)^2 - 4\alpha\gamma}], \tag{2.15}$$

which are real, positive, and distinct. It follows that $\mathbf{A}(\gamma)$ is diagonalizable. Introducing the expansions

$$\widetilde{\mathbf{p}}(x,0) = c_+(x)\mathbf{v}_+(\gamma) + c_-(x)\mathbf{v}_-(\gamma), \tag{2.16}$$

we obtain the pair of uncoupled equations

$$D\frac{d^2c_+}{dx^2} - \lambda_+(\gamma)c_+(x) = -\Gamma_+(\gamma)\delta(x), \tag{2.17a}$$

$$D\frac{d^2c_-}{dx^2} - \lambda_-(\gamma)c_-(x) = -\Gamma_-(\gamma)\delta(x), \tag{2.17b}$$

where

$$\Gamma_\pm(\gamma) \equiv \frac{\widehat{\mathbf{v}}_\pm(\gamma)\cdot\mathbf{e}_0}{\widehat{\mathbf{v}}_\pm(\gamma)\cdot\mathbf{v}_\pm(\gamma)} = \frac{[\alpha - \lambda_\pm(\gamma)]\rho_0 + \alpha\rho_1}{[\alpha - \lambda_\pm(\gamma)]^2 + \alpha\beta}. \tag{2.18}$$

Solving these equations along lines identical to those of the nonswitching case shows that

$$c_\pm(x) = \frac{\Gamma_\pm(\lambda)}{\sqrt{D\lambda_\pm(\lambda)}}e^{-\sqrt{\lambda_\pm(\lambda)/D}x}, \tag{2.19}$$

and

$$q(x) \equiv \gamma\,\widetilde{p}_0(x,0) = \gamma\left\{[\alpha - \lambda_+(\gamma)]\frac{\Gamma_+(\gamma)}{\sqrt{D\lambda_+(\gamma)}}e^{-\sqrt{\lambda_+(\gamma)/D}x} + [\alpha - \lambda_-(\gamma)]\frac{\Gamma_-(\gamma)}{\sqrt{D\lambda_-(\gamma)}}e^{-\sqrt{\lambda_-(\gamma)/D}x}\right\}. \tag{2.20}$$

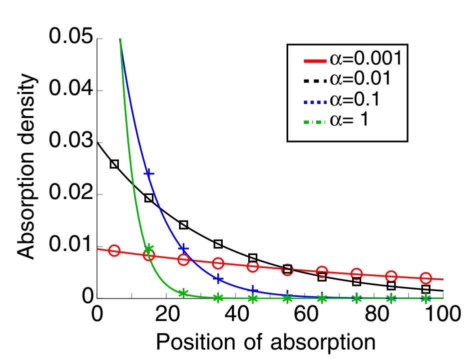

FIG. 2. Absorption density $q(x)$ as a function of absorption position x. The solid curves are determined from Eq. (2.20) and the marks are the results from Monte Carlo simulations. We take $\beta = 1$, $\gamma = 0.1$, $D = 1$, and α varies.

In particular, if $\alpha+\beta \gg \gamma$, then $\lambda_+ \gg \lambda_-$ and $\lambda_-(\gamma) \approx [\alpha/(\alpha+\beta)]\gamma$. Hence, in the fast switching regime

$$q(x) \approx \sqrt{\frac{\gamma_{\text{eff}}}{D}} e^{-\sqrt{\gamma_{\text{eff}}/D}x}, \tag{2.21}$$

where

$$\gamma_{\text{eff}} = \frac{\alpha}{\alpha+\beta}\gamma \tag{2.22}$$

is an effective absorption rate. This is equal to the original absorption rate multiplied by the mean proportion of time the Brownian particle or gate is in the state $k=0$. Plots of the spatial decay of $q(x)$ for different values of α and other parameters fixed are shown in Fig. 2. It can be seen that large α increases the decay rate, whereas small α reduces the effects of absorption at sites close to the source at $x=0$ so that resources can reach regions further into the domain.

III. POPULATION OF BROWNIAN PARTICLES DIFFUSING IN A STOCHASTICALLY GATED ABSORBING ENVIRONMENT

So far we have focused on a single Brownian particle diffusing in a stochastically gated absorbing environment. We now turn to the case of a population of noninteracting Brownian particles diffusing in such an environment. In contrast to the single-particle case, the two scenarios shown in Fig. 1 are no longer equivalent. That is, if each particle randomly switches conformational state, then there are no statistical correlations between the particles, and one can simply carry over the analysis of Sec. II. On the other hand, if the gate itself randomly switches state, then correlations arise from the fact that all the particles diffuse in the same switching environment. We will consider the latter in this section.

Consider an ensemble of identical, independent Brownian particles labeled by $i=1,\ldots,\mathcal{N}$ with position variables $X_i(t)$, $X_i(0)=0$, all being subject to the same randomly switching environment; see Fig. 3. Consider a single realization of the stochastic switching process, $\sigma(t)=\{k(\tau),0\leqslant\tau\leqslant t\}$. Take the thermodynamic limit $\mathcal{N}\to\infty$, and let $P(x,t)$ denote the probability density of particles in state x at time t given the particular realization $\sigma(t)$. The population density evolves according to the stochastic Fokker-Planck (FP) equation

$$\frac{\partial P(x,t)}{\partial t} = D\frac{\partial^2 P(x,t)}{\partial x^2} - \gamma[1-k(t)]P(x,t), \quad x>0, \tag{3.1}$$

with $P(x,0)=\delta(x)$ and a reflecting boundary at $x=0$. We also introduce the corresponding absorption density $Q(x,t)$,

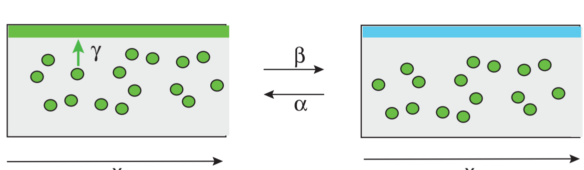

FIG. 3. Population of Brownian particles diffusing in the same environment with stochastically gated absorption.

with

$$\frac{\partial Q(x,t)}{\partial t} = \gamma[1-k(t)]P(x,t) \tag{3.2}$$

and $Q(x,0)=0$. Noting that the densities $P(x,t)$ and $Q(x,t)$ are random fields with respect to different realizations of the dynamic gate, we will average with respect to these realizations and analyze the large-time limit.

We will proceed by extending recent work on diffusion processes with randomly switching boundary conditions [34,36,37,39]. In these studies a method was developed for deriving a closed set of equations for equal-time moments of the stochastic fields. For our gating model, the first-order moments are defined according to

$$\overline{p}_k(x,t) \equiv \mathbb{E}[P(x,t)1_{k(t)=k}], \quad \overline{q}(x,t) \equiv \mathbb{E}[Q(x,t)], \tag{3.3a}$$

and the second-order moments are

$$C_k(x,y,t) \equiv \mathbb{E}[P(x,t)P(y,t)1_{k(t)=k}], \tag{3.3b}$$

$$R_k(x,y,t) \equiv \mathbb{E}[P(x,t)Q(y,t)1_{k(t)=k}], \tag{3.3c}$$

$$S(x,y,t) \equiv \mathbb{E}[Q(x,t)Q(y,t)], \tag{3.3d}$$

where expectation is taken with respect to realizations $\sigma(t)$. Here $1_{k(t)=k}$ is an indicator function which is equal to one if $k(t)=k$ and is zero otherwise. Higher-order moments are similarly defined, for example,

$$C_k^{(r)}(x_1,\ldots,x_r,t) \equiv \mathbb{E}[P(x_1,t)\cdots P(x_r,t)1_{k(t)=k}]. \tag{3.4}$$

From a computational perspective, the various moments can be determined by running multiple realizations $\sigma_1,\ldots,\sigma_\chi$ of the population model. Each trial σ_j yields a probability density $P_{\sigma_j}^{\mathcal{N}}(x,t)$, whose accuracy will depend on the population size $\mathcal{N}$. Averaging with respect to the realizations then yields an approximation of the first-order moment,

$$\overline{p}(x,t) \equiv \overline{p}_0(x,t) + \overline{p}_1(x,t) \approx \chi^{-1}\sum_{j=1}^{\chi} P_{\sigma_j}^{\mathcal{N}}(x,t).$$

Similarly,

$$C(x,y,t) \equiv C_0(x,y,t) + C_1(x,y,t) \approx \chi^{-1}\sum_{j=1}^{\chi} P_{\sigma_j}^{\mathcal{N}}(x,t)P_{\sigma_j}^{\mathcal{N}}(y,t).$$

The existence of correlations induced by the switching environment means that

$$C_k(x,y,t) \neq \overline{p}_k(x,t)\overline{p}_k(y,t),$$

for example.

In the Appendix, we show how to derive a closed set of equations for the first and second moments following along lines analogous to those in [34]. We find that the first-order moments u_k evolve as

$$\frac{\partial \overline{p}_k}{\partial t} = D\frac{\partial^2 \overline{p}_k}{\partial x^2} - \gamma(1-k)\overline{p}_k + \sum_{m=0,1} W_{km}\overline{p}_m, \tag{3.5}$$

with Neumann boundary conditions at $x=0$. Here $\mathbf{W}$ is the generator of the two-state Markov chain underlying the stochastic gate:

$$\mathbf{W} = \begin{pmatrix} -\beta & \alpha \\ \beta & -\alpha \end{pmatrix}. \tag{3.6}$$

Moreover,

$$\frac{\partial \overline{q}}{\partial t} = \gamma \overline{p}_0(x,t). \tag{3.7}$$

Formally speaking, Eqs. (3.5) are identical to Eqs. (2.11a) and (2.11b) for the single-particle probability densities $p_k(x,t)$. It follows that we can identify $\overline{q}(x,t)$ with $q(x,t)$. [Note that the first-order moments of the population model are not always equivalent to the probability densities of the single-particle model, since there is a much wider class of boundary conditions that one can impose on the population model (3.1). This reflects the fact that particle conservation need not hold at the population level. For example, one could impose a constant nonzero flux of particles at $x=0$; see also the discussion at the beginning of Sec. II.]

Similarly, it can be shown that

$$\frac{\partial C_k}{\partial t} = D\frac{\partial^2 C_k}{\partial x^2} + D\frac{\partial^2 C_k}{\partial y^2} - 2\gamma(1-k)C_k + \sum_{m=0,1} W_{km}C_m. \tag{3.8}$$

These are supplemented by the initial conditions

$$C_k(x,y,0) = \overline{p}_k(x,0)\overline{p}_k(y,0) \tag{3.9}$$

and boundary conditions

$$\left.\frac{\partial C_k(x,y,t)}{\partial x}\right|_{x=0} = 0 = \left.\frac{\partial C_k(x,y,t)}{\partial y}\right|_{y=0}, \quad k=0,1. \tag{3.10}$$

Equations (3.8) for the second-order moments $C_k(x,y,t)$ are identical in form to the CK equation that would be written down for the joint probability density of two Brownian particles with positions x and y at time t, evolving in the same randomly switching environment. More generally, $C^{(r)}$ is related to the joint probability density of r particles. However, we are mainly interested in the statistics of the absorption distribution in the large-t limit, in particular, the variance in the distribution across multiple realizations of the gate. The latter is given by (assuming it exists)

$$\mathrm{Var}[Q(x)] = \lim_{t\to\infty} S(x,x,t) - q(x)^2, \tag{3.11}$$

where $q(x)$ is the solution (2.20), It turns out that the second-order moment distribution $S(x,y,t)$ is determined by $R_k(x,y,t)$, which itself couples to $C_k(x,y,t)$; see the Appendix. That is,

$$\frac{\partial R_k(x,y,t)}{\partial t} = D\frac{\partial^2 R_k(x,y,t)}{\partial x^2} - \gamma(1-k)R_k(x,y,t) + \gamma(1-k)C_k(x,y,t) + \sum_{m=0,1} W_{km}R_m(x,y,t), \tag{3.12}$$

and

$$\frac{\partial S(x,y,t)}{\partial t} = \gamma R_0(x,y,t) + \gamma R_0(y,x,t). \tag{3.13}$$

Equations (3.12) and (3.13) are supplemented by the conditions $R_k(x,y,0) = S(x,y,0) = 0$ and $\partial_x R_k(0,y,t) = 0$. Combining Eqs. (3.11) and (3.13) implies that

$$\mathrm{Var}[Q(x)] = 2\gamma \widetilde{R}_0(x,x,0) - q(x)^2, \tag{3.14}$$

where $\widetilde{R}(x,y,s)$ is the Laplace transform of $R(x,y,t)$.

Since equation (3.12) is coupled to the two-point correlation $C_0(x,y,t)$, we first solve Eq. (3.8) with $C_k(x,y,0) = \delta(x)\delta(y)\rho_k$ and

$$\left.\frac{\partial C_k}{\partial x}\right|_{x=0} = \left.\frac{\partial C_k}{\partial y}\right|_{y=0} = 0.$$

Proceeding as in Sec. II B, we apply the Laplace transform to Eq. (3.8), set $s=0$, and write it in the matrix form

$$D\Delta\widetilde{\mathbf{C}}(x,y,0) - \mathbf{A}(2\gamma)\widetilde{\mathbf{C}}(x,y,0) = -\mathbf{e}_0\delta(x)\delta(y) \tag{3.15}$$

for $\widetilde{\mathbf{C}} \equiv [\widetilde{C}_0,\widetilde{C}_1]^\top$. The matrix $\mathbf{A}(2\gamma)$ is given by Eq. (2.14) except that $\gamma \to 2\gamma$. Following Eq. (2.16), we introduce the expansion

$$\widetilde{\mathbf{C}}(x,y,0) = f_+(x,y)\mathbf{v}_+(2\gamma) + f_-(x,y)\mathbf{v}_-(2\gamma),$$

which yields the decoupled equations

$$D\Delta f_\pm(x,y) - \lambda_\pm(2\gamma)f_\pm(x,y) = -\Gamma_\pm(2\gamma)\delta(x)\delta(y). \tag{3.16}$$

Equations (3.16) can be solved using Green's functions and the method of images. Let $\mathbf{x} \equiv (x,y)$ and set $|\mathbf{x}| = r$. First, note that the fundamental solution $\mathcal{G}_\mu$ of the two-dimensional modified Helmholtz equation satisfies (in polar coordinates)

$$\frac{\partial^2 \mathcal{G}_\mu}{\partial r^2} + \frac{1}{r}\frac{\partial \mathcal{G}_\mu}{\partial r} - \mu^2\mathcal{G}_\mu = -\delta(r).$$

The solution is given by

$$\mathcal{G}_\mu(r) = \frac{1}{2\pi}K_0(\mu r),$$

where K_0 is a modified Bessel function of the *third* kind. Next we introduce the source point $\xi \equiv (x_0,y_0)$ and the mirror image vectors $\xi_1 \equiv (-x_0,y_0), \xi_2 \equiv (-x_0,-y_0), \xi_3 \equiv (x_0,-y_0)$. It then follows from the method of images that the Neumann Green's function of the modified Helmholtz equation in the first quadrant of $\mathbb{R}^2$ is

$$G_\mu(\mathbf{x},\xi) = \frac{1}{2\pi}[K_0(\mu|\mathbf{x}-\xi|) + K_0(\mu|\mathbf{x}-\xi_1|) + K_0(\mu|\mathbf{x}-\xi_2|) + K_0(\mu|\mathbf{x}-\xi_3|)]. \tag{3.17}$$

Finally, expressing $f_\pm$ in terms of $G_{\mu_\pm}$, where $\mu_\pm = \sqrt{\lambda_\pm(2\gamma)/D}$, gives

$$\widetilde{C}_0(x,y,0) = \frac{1}{D}\{[\alpha - \lambda_+(2\gamma)]\Gamma_+(2\gamma)G_{\mu_+}(\mathbf{x},0) + [\alpha - \lambda_-(2\gamma)]\Gamma_-(2\gamma)G_{\mu_-}(\mathbf{x},0)\}. \tag{3.18}$$

Returning to Eq. (3.12), we now seek to analyze $R_k(x,y,t)$. Again we apply the Laplace transform and set $s=0$ to obtain

$$D\frac{\partial^2\widetilde{\mathbf{R}}}{\partial x^2} - \mathbf{A}(\gamma)\widetilde{\mathbf{R}} = -\gamma\widetilde{C}_0(1,0)^\top, \qquad \widetilde{\mathbf{R}} \equiv (\widetilde{R}_0,\widetilde{R}_1)^T.$$

We introduce the decomposition

$$\widetilde{\mathbf{R}}(x,y,0) = \mathbf{v}_+(\gamma)r_+(x,y) + \mathbf{v}_-(\gamma)r_-(x,y),$$

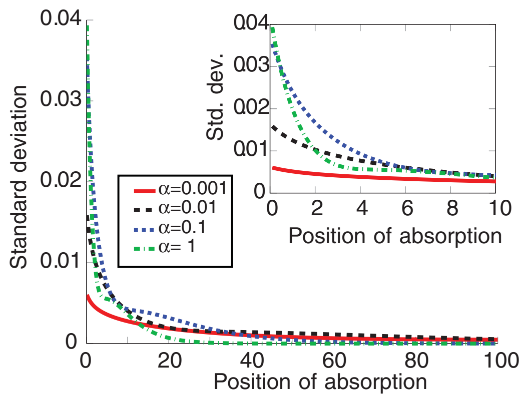

FIG. 4. Standard deviation of absorption density $Q(x)$ over different realizations of the stochastic gate using (3.14). We take $\beta = 1, \gamma = 0.1, D = 1$, and α varies. The inset magnifies absorption positions $x \in [0,10]$.

with

$$D\frac{\partial^2 r_\pm}{\partial x^2} - \lambda_\pm(\gamma) r_\pm = -\gamma \overline{\Gamma}_\pm(\gamma)\widetilde{C}_0$$

and $\overline{\Gamma}_\pm(\gamma)$ given by Eq. (2.18) for $\mathbf{e}_0 = (1,0)^\top$. The solutions are immediately

$$r_\pm(x,y) = \frac{\gamma\overline{\Gamma}_\pm(\gamma)}{2\sqrt{\lambda_\pm(\gamma)D}}\int_0^\infty \times [e^{-\sqrt{\lambda_\pm(\gamma)/D}|x-\xi|} + e^{-\sqrt{\lambda_\pm(\gamma)/D}|x+\xi|}]\widetilde{C}_0(\xi,y,0)d\xi, \tag{3.19}$$

and

$$\widetilde{R}_0(x,y,0) = [\alpha - \lambda_+(\gamma)]r_+(x,y) + [\alpha - \lambda_-(\gamma)]r_-(x,y). \tag{3.20}$$

In Fig. 4, we use (3.14) to plot the standard deviation of $Q(x)$ over realizations of the stochastic gate. Interestingly, this plot shows that the standard deviation of $Q(x)$ is nonmonotonic in the switching rate $\alpha = \beta$ for certain values of $x > 0$. Nevertheless, we will see in Sec. IV that $Q(x)$ becomes deterministic in the fast switching limit, and hence its standard deviation vanishes if $\alpha \gg 1, \beta \gg 1$.

IV. EXPLICIT STOCHASTIC SOLUTION

Our analysis of a population of Brownian particles diffusing in the same randomly absorbing environment required studying the piecewise-deterministic partial differential equation (PDE) (3.1). Another way to view this equation is as an example of a parabolic PDE with a stochastically gated decay rate. In this section we construct an explicit solution of this more general class of stochastic PDEs and show how r-point correlations can be analyzed using previous studies of stochastically gated compartments. We then relate this analysis to the particular case of diffusion in absorbing environments.

Suppose $P(x,t)$ satisfies the evolution equation

$$\frac{\partial P(x,t)}{\partial t} = \mathbb{L}_x P(x,t) - \gamma[1-k(t)]P(x,t), \quad x \in \Omega \subset \mathbb{R}^d, \tag{4.1}$$

where $\mathbb{L}_x$ is a linear differential operator and $k(t) \in \{0,1\}$ evolves according to the two-state Markov chain of previous sections. Equation (4.1) is supplemented by appropriate boundary conditions on $\partial\Omega$ and an initial condition $P(x,0) = v_0(x)$. We now observe that P can be decomposed as

$$P(x,t) = e^{-\gamma\theta(t)}v(x,t), \tag{4.2}$$

where $\theta(t)$ is the residence time of $k(t)$ in state 0,

$$\theta(t) \equiv \int_0^t [1-k(\tau)]\,d\tau,$$

and $v(x,t)$ is the deterministic solution to the initial boundary-value problem

$$\frac{\partial v}{\partial t} = \mathbb{L}_x v, \quad x \in \Omega, \tag{4.3}$$

with the same boundary conditions and initial condition $v(x,0) = v_0(x)$. With the representation (4.2), we see that understanding the statistics of P reduces to understanding the statistics of $e^{-\gamma\theta(t)}$. The latter problem was originally analyzed by Kubo [40] in the study of spectral line broadening in a quantum system and subsequently extended to chemical rate processes with dynamical disorder by Zwanzig [41]. It has subsequently arisen in other contexts such as modeling the exchange of particles to and from a well-mixed domain within the plasma membrane through a randomly opening and closing channel [42]. Here we apply such methods within the context of the stochastic PDE. We first note that in the fast switching limit, $\alpha + \beta \to \infty$ with α/β fixed, we have that with probability one,

$$\theta(t) \to \rho_0 t, \quad \overline{\rho}_0 = \frac{\alpha}{\alpha+\beta}.$$

[Note that $(\overline{\rho}_0, 1-\overline{\rho}_0)^\top$ is the stationary measure of the matrix $\mathbf{W}$.] Hence, in this fast switching limit we have that with probability one

$$P(x,t) \to e^{-\gamma\rho_0 t}v(x,t).$$

That is, for fast switching the problem reduces to the problem with an effective static decay rate $\rho_0\gamma$ (see also Sec. II B). In addition to this almost sure limiting behavior, we can use (4.2) to calculate the r-point correlations of P,

$$\mathbb{E}\left[\prod_{j=1}^r P(x_j,t_j)\right] = \left[\prod_{j=1}^r v(x_j,t_j)\right]\mathbb{E}\left[\prod_{j=1}^r e^{-\gamma\theta(t_j)}\right], \tag{4.4}$$

for $x_1,\ldots,x_r,t_1,\ldots,t_r \in [0,\infty)$. For the moment, we do not restrict ourselves to equal-time correlations ($t_i = t$ for all i), and we focus on the cases $r = 1$ and $r = 2$.

First observe that $Y(t) \equiv e^{-\gamma\theta(t)}$ is a piecewise-deterministic Markov process that satisfies

$$\dot{Y}(t) = -\gamma[1-k(t)]Y(t).$$

Hence, the probability density function of $Y(t)$,

$$\mathcal{P}_k(y,t)dy = \mathbb{P}(Y(t) \in (y,y+dy), k(t) = k),$$

satisfies the forward differential CK equation

$$\frac{\partial}{\partial t}\mathcal{P}_0 = -\frac{\partial}{\partial x}(-\gamma y\mathcal{P}_0) - \beta\mathcal{P}_0 + \alpha\mathcal{P}_1, \tag{4.5}$$

$$\frac{\partial}{\partial t}\mathcal{P}_1 = \beta\mathcal{P}_0 - \alpha\mathcal{P}_1. \tag{4.6}$$

From Eqs. (4.5) and (4.6), it follows that the first moments of $Y(t)$,

$$m_k(t) \equiv \mathbb{E}[Y(t)1_{k(t)=k}],$$

satisfy the linear ordinary differential equations (ODEs)

$$\frac{d}{dt}\begin{pmatrix} m_0 \\ m_1 \end{pmatrix} = -\mathbf{A}(\gamma)\begin{pmatrix} m_0 \\ m_1 \end{pmatrix}, \tag{4.7}$$

with $\mathbf{A}(\gamma)$ given by Eq. (2.14), and the initial conditions, $m_k(0) = \rho_k$, assuming $\mathbb{P}(k(0) = k) = \rho_k$. Hence, we have that

$$\begin{pmatrix} m_0(t) \\ m_1(t) \end{pmatrix} = e^{-\mathbf{A}(\gamma)t}\begin{pmatrix} \rho_0 \\ \rho_1 \end{pmatrix}. \tag{4.8}$$

This equation can be solved by expanding in terms of the eigenvectors $\mathbf{v}_\pm$ (or equivalently diagonalizing the matrix $\mathbf{A}$). We thus obtain the result

$$\mathbf{m}(t) = \Gamma_+(\gamma)e^{-\lambda_+(\gamma)t}\mathbf{v}_+(\gamma) + \Gamma_-(\gamma)e^{-\lambda_-(\gamma)t}\mathbf{v}_-(\gamma). \tag{4.9}$$

Hence, the first moment of P is

$$\mathbb{E}[P(x,t)] = v(x,t)[m_0(t) + m_1(t)]. \tag{4.10}$$

To compute the two-point correlation of P, we need to calculate the two-point correlations of Y,

$$m^{(2)}_{kj}(t,t_0) \equiv \mathbb{E}[Y(t)1_{k(t)=k}Y(t_0)1_{k(t_0)=j}],$$

for $t \geqslant t_0 \geqslant 0$ and $k,j \in \{0,1\}$. It is straightforward to show that $m^{(2)}_{kj}(t,t_0)$ satisfies (4.7) with initial conditions at $t = t_0$ given by

$$m^{(2)}_{kj}(t_0,t_0) = \delta_{k,j}m^{(2)}_j(t_0),$$

where $\delta_{k,j}$ is the Kronecker δ and

$$m^{(2)}_j(t) = \mathbb{E}[e^{-2\gamma\theta(t)}1_{k(t)=j}].$$

Hence, we have that

$$\begin{pmatrix} m^{(2)}_{0j}(t,t_0) \\ m^{(2)}_{1j}(t,t_0) \end{pmatrix} = e^{-\mathbf{A}(\gamma)(t-t_0)}\begin{pmatrix} \delta_{0,j}m^{(2)}_0(t_0) \\ \delta_{1,j}m^{(2)}_1(t_0) \end{pmatrix}.$$

Moreover, $\mathbf{m}^{(2)} = (m^{(2)}_0, m^{(2)}_1)^\top$ evolves according to the equation

$$\frac{d}{dt}\begin{pmatrix} m^{(2)}_0 \\ m^{(2)}_1 \end{pmatrix} = -\mathbf{A}(2\gamma)\begin{pmatrix} m^{(2)}_0 \\ m^{(2)}_1 \end{pmatrix}, \tag{4.11}$$

which implies

$$\mathbf{m}^{(2)}(t) = \Gamma_+(2\gamma)e^{-\lambda_+(2\gamma)t}\mathbf{v}_+(2\gamma) \tag{4.12}$$

$$+\Gamma_-(2\gamma)e^{-\lambda_-(2\gamma)t}\mathbf{v}_-(2\gamma). \tag{4.13}$$

Combining these results, the two-point correlations of P are given by

$$\mathbb{E}[P(x_2,t_2)P(x_1,t_1)] = v(x_2,t_2)v(x_1,t_1)\sum_{j_2,j_1\in\{0,1\}} m^{(2)}_{j_2j_1}(t_2,t_1),$$

where $t_2 \geqslant t_1 \geqslant 0$.

The analysis simplifies in the case of the equal-time correlations

$$\sum_{k=0,1} C^{(r)}_k(x_1,\ldots,x_r,t) \equiv \mathbb{E}\left[\prod_{j=1}^r P(x_j,t)\right] = \left[\prod_{j=1}^r v(x_j,t)\right]\mathbb{E}[e^{-r\gamma\theta(t)}],$$

Generalizing Eq. (4.11), we find that

$$\mathbb{E}[e^{-r\gamma\theta(t)}] = m^{(r)}_0(t) + m^{(r)}_1(t), \tag{4.14}$$

where

$$\frac{d}{dt}\begin{pmatrix} m^{(r)}_0 \\ m^{(r)}_1 \end{pmatrix} = -\mathbf{A}(r\gamma)\begin{pmatrix} m^{(r)}_0 \\ m^{(r)}_1 \end{pmatrix}. \tag{4.15}$$

Hence,

$$\sum_{k=0,1} C^{(r)}_k(x_1,\ldots,x_r,t) = \left[\prod_{j=1}^r v(x_j,t)\right]\left[m^{(r)}_0(t) + m^{(r)}_1(t)\right]. \tag{4.16}$$

An alternative way to analyze the equal-time correlations is to derive PDEs for the moments along the lines outlined in Sec. III and the Appendix. For the general PDE (4.1) we find that $C^{(r)}_k$ satisfies the rth-order PDE

$$\frac{\partial C^{(r)}_k}{\partial t} = \sum_{j=1}^r \mathbb{L}_{x_j}C^{(r)}_k - \sum_m A_{km}(r\gamma)C^{(r)}_m. \tag{4.17}$$

This has a solution of the form

$$C^{(r)}_k(x_1,\ldots,x_r,t) = v^{(r)}(x_1,\ldots,x_r,t)m^r_k(t),$$

with $v^{(r)}$ satisfying the equation

$$\frac{\partial v^{(r)}}{\partial t} = \sum_{j=1}^r \mathbb{L}_{x_j}v^{(r)}.$$

The latter has the separable solution

$$v^{(r)}(x_1,\ldots,x_r,t) = \prod_{j=1}^r v(x_j,t),$$

and thus we recover Eq. (4.16).

Let us now return to the specific PDE given by Eq. (3.1). In this case,

$$v(x,t) \equiv \frac{2}{\sqrt{4\pi Dt}}e^{-x^2/(4Dt)}.$$

Substituting Eq. (4.9) into Eq. (4.10) and taking the limit $t \to \infty$ then recovers the solution (2.20) for $q(x)$. This follows from the Laplace transform

$$\mathcal{L}[v(x,t)e^{-\lambda t}](s) = \frac{1}{\sqrt{(\lambda+s)D}}e^{-\sqrt{(\lambda+s)/D}x}.$$

Similarly, using Eq. (4.16) for $r=2$ and Eq. (4.13), we see that

$$C_0(x,y,t)+C_1(x,y,t) = \frac{1}{\pi Dt}e^{-[x^2+y^2]/(4Dt)}[\Gamma_+(2\gamma)e^{-\lambda_+(2\gamma)t}\mathbf{v}_+(2\gamma) + \Gamma_-(2\gamma)e^{-\lambda_-(2\gamma)t}\mathbf{v}_-(2\gamma)].$$

Laplace transforming this equation using the identity

$$\mathcal{L}\left(\frac{1}{2Dt}e^{-x^2/4Dt-\lambda t}\right) = \frac{1}{D}K_0(x\sqrt{[s+\lambda]/D})$$

and setting $s=0$ then recovers the solution (3.18). One possible advantage of the moments methods developed in Sec. III is that one can determine derived quantities such as $\mathbb{E}[Q(x,t)Q(y,t)]$ by solving the auxiliary Eq. (3.12) for the equal-time moments $R_k(x,y,t)$. In terms of the direct method above, one has to evaluate the double integral

$$\mathbb{E}[Q(x,t)Q(y,t)] = \gamma^2\int_0^t\int_0^t v(x,\tau_2)v(y,\tau_1)m_{00}^{(2)}(\max(\tau_2,\tau_1), (\min(\tau_2,\tau_1))\,d\tau_1\,d\tau_2.$$

Another advantage of the moments method is that it can handle heterogeneous absorption.

V. HETEROGENEOUS ABSORPTION

A classical problem in the theory of diffusion-limited reactions is analyzing the effective rate of absorption of Brownian particles moving in a medium with periodically or randomly distributed static traps [1,3,5,7]. In cases where Smoluchowski mean-field theory holds, one can show that the survival probability of the diffusing particles exhibits exponential decay at a rate that depends on the concentration of traps. In other words, the ensemble of traps may be treated as a uniform (homogenized) absorbing medium. This is the approach taken in previous sections. Here we turn to the case of a spatially heterogeneous absorbing medium consisting of N spatially localized traps at positions x_n, $n=1,\ldots,N$. For simplicity, we will assume that the stochastic gating of the traps is synchronized so that there is a single gating variable $k(t)\in\{0,1\}$. If each trap had its own independent gate with discrete state $k_n(t)\in\{0,1\}$, then switching would be described by a Markov chain with 2^N states.

The population model of Sec. III now evolves according to the stochastic equation

$$\frac{\partial P(x,t)}{\partial t} = D\frac{\partial^2 P(x,t)}{\partial x^2} - \gamma_d[1-k(t)]\sum_{n=1}^N \delta(x-x_n)P_n(t) \tag{5.1}$$

for $x>0$, with $P_n(t)=P(x_n,t)$ and a reflecting boundary at $x=0$. Moreover,

$$\frac{\partial Q(x,t)}{\partial t} = \gamma_d[1-k(t)]\sum_{n=1}^N \delta(x-x_n)P_n(t), \tag{5.2}$$

and $Q(x,0)=0$. Note that γ_d has the units of velocity rather than inverse time. It follows that we can set

$$Q(x,t) = \sum_{n=1}^N Q_n(t)\delta(x-x_n),$$

with

$$\frac{dQ_n}{dt} = \gamma_d[1-k(t)]P_n(t).$$

For the sake of illustration, we will focus on the first-order moment equations for $p_k(x,t)$ and $q(x,t)$ defined by Eq. (3.25a), after dropping the bars. After setting

$$p_{k,n}(t) = p_k(x_n,t) = \mathbb{E}[P(x_n,t)1_{k(t)=k}],$$

we have

$$\frac{\partial p_k}{\partial t} = D\frac{\partial^2 p_k}{\partial x^2} - \sum_{l=0,1}W_{kl}p_l - \gamma_d\delta_{k,0}\sum_{n=1}^N\delta(x-x_n)p_{0,n}(t) \tag{5.3}$$

and

$$\frac{dq_n}{dt} = \gamma_d p_{0,n}(t). \tag{5.4}$$

We want to calculate

$$q_n^\infty = \lim_{t\to\infty} q_n(t) = \gamma_d\int_0^\infty p_{0,n}(\tau)d\tau = \gamma_d\widetilde{p}_{0,n}(0). \tag{5.5}$$

Laplace transforming Eq. (5.3) with $p_k(x,0)=\rho_k\delta(x)$, we have

$$D\frac{d^2\widetilde{p}_k}{dx^2} - \sum_{l=0,1}W_{kl}\widetilde{p}_l - s\widetilde{p}_k = -\delta(x)\rho_k + \gamma_d\delta_{k,0}\sum_{n=1}^N\delta(x-x_n)\widetilde{p}_{0,n}(s), \tag{5.6}$$

supplemented by the boundary condition

$$\left.\frac{d\widetilde{p}_k}{dx}\right|_{x=0} = 0.$$

Summing both sides of Eq. (5.6) with respect to $k\in\{0,1\}$ gives

$$D\frac{\partial^2\widetilde{p}}{\partial x^2} - s\widetilde{p} = -\delta(x) + \gamma_d\sum_{n=1}^N\delta(x-x_n)\widetilde{p}_{0,n}(s), \tag{5.7}$$

with $\widetilde{p}_m(s) = \widetilde{p}_{0,m}(s) + \widetilde{p}_{1,m}(s)$. Introduce the Neumann Green's function $G(y,x;s)$ with

$$D\frac{d^2G(y,x;s)}{dy^2} - sG(y,x;s) = -\delta(x-y), \quad x,y\in(0,\infty), \tag{5.8}$$

and $\partial_y G = 0$ at $y = 0$. Solving this equation yields

$$G(y,x;s) = \frac{1}{2}\sqrt{\frac{1}{sD}}[e^{-\sqrt{s/D}|x-y|} + e^{-\sqrt{s/D}(x+y)}]. \quad (5.9)$$

An application of Green's theorem then leads to the implicit equation

$$\begin{aligned}\widetilde{p}(x,s) &= \int_0^\infty dy G(y,x;s) \\ &\quad \times \left[\delta(y) - \gamma_d \sum_{n=1}^N \delta(y-x_n)\widetilde{p}_{0,n}(s)\right] \\ &= G(0,x;s) - \gamma_d \sum_{n\geqslant 1} G(x_n,x;s)\widetilde{p}_{0,n}(s). \quad (5.10)\end{aligned}$$

Return to Eq. (5.6) and set $k = 0$:

$$\begin{aligned}D\frac{d^2\widetilde{p}_0}{dx^2} &- (s+\alpha+\beta)\widetilde{p}_0 \\ &= -\delta(x)\rho_0 - \alpha\widetilde{p} + \gamma_d \sum_{n=1}^N \delta(x-x_n)\widetilde{p}_{0,n}(s). \quad (5.11)\end{aligned}$$

This equation can be solved using the Neumann Green's function $\widehat{G}(x,y;s) = G(x,y,s+\alpha+\beta)$:

$$\begin{aligned}\widetilde{p}_0(x,s) &= \widehat{G}(0,x;s)\rho_0 - \gamma_d \sum_{n\geqslant 1} \widehat{G}(x_n,x;s)\widetilde{p}_{0,n}(s) \\ &\quad + \alpha \int_0^\infty \widehat{G}(y,x;s)\widetilde{p}(y,s)dy.\end{aligned}$$

Finally, substituting for $\widetilde{p}(y,s)$ using Eq. (5.10) and setting $x = x_m$, we obtain the matrix equation

$$\begin{aligned}\widetilde{p}_{0,m}(s) &= \widehat{G}_{0m}(s)\rho_0 + \alpha\widehat{H}_{0m}(s) \\ &\quad - \gamma_d \sum_{n=1}^N [\widehat{G}_{nm}(s) + \alpha\widehat{H}_{nm}(s)]\widetilde{p}_{0,n}(s), \quad (5.12)\end{aligned}$$

where $\widehat{G}_{nm}(s) = \widehat{G}(x_n,x_m;s)$,

$$\widehat{H}_{nm}(s) = \int_0^\infty G(x_n,y;s)\widehat{G}(y,x_m;s)dy, \quad (5.13)$$

and $x_0 = 0$.

In order to derive a matrix equation for the q_n^∞, we note that in the limit $s \to 0$,

$$\widehat{G}_{nm}(s) \to G_{nm}(\alpha+\beta)$$

and

$$\widehat{H}_{nm}(s) \to \frac{A_m}{\sqrt{sD}}, \quad A_m = \int_0^\infty G(y,x_m;\alpha+\beta)dy.$$

Introduce the approximation

$$\gamma_d \widetilde{p}_{0,n}(s) = q_n^\infty + C_n\sqrt{s} + \text{h.o.t.}$$

where h.o.t. is higher order terms.

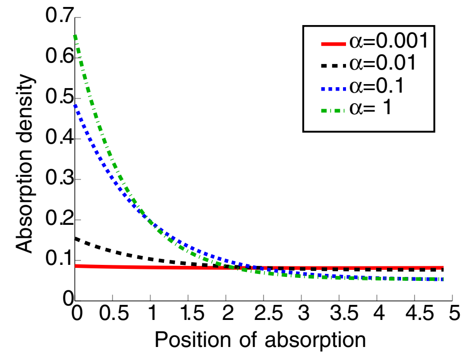

FIG. 5. Absorption density in the case of heterogeneous, gated absorption. For spatially localized traps at positions $x_n = n\Delta x$ for $\Delta x = 0.1$ and $n = 0,\ldots,100$, the curves are the effective absorption density, $q_n^\infty/\Delta x$ with q_n^∞ in (5.16). We take $\beta = \gamma_d = 0.1$, $D = 1$, and α varies.

Substituting into Eq. (5.12) gives

$$\begin{aligned}q_m^\infty &= \frac{\alpha\gamma_d A_m}{\sqrt{sD}}\left[1 - \sum_{n=1}^N q_n^\infty\right] \\ &\quad + \gamma_d\left[G_{0m}(\alpha+\beta)\rho_0 - \sum_{n=1}^N G_{nm}(\alpha+\beta)q_n^\infty\right] \\ &\quad - \frac{\alpha\gamma_d A_m}{\sqrt{D}}\sum_{n=1}^N C_n + \text{h.o.t.} \quad (5.14)\end{aligned}$$

The singular term vanishes provided that we impose the normalization

$$1 = \sum_{n=1}^N q_n^\infty, \quad (5.15)$$

and equating the $O(1)$ terms leads to the matrix equation

$$\begin{aligned}\sum_{n=1}^N \mathcal{A}_{mn}q_n^\infty &\equiv q_m^\infty + \gamma_d \sum_{n=1}^N G_{nm}(\alpha+\beta)q_n^\infty \\ &= \gamma_d G_{0m}(\alpha+\beta)\rho_0 - \Gamma A_m, \quad (5.16)\end{aligned}$$

with the unknown constant

$$\Gamma = \frac{\alpha\gamma_d}{\sqrt{D}}\sum_{n=1}^N C_n$$

determined by the normalization condition (5.15).

Solving (5.16) numerically, Fig. 5 shows that gated absorption can mitigate attenuation in the case of spatially heterogeneous traps, just as in the case of a spatially uniform trap considered in previous sections.

VI. DISCUSSION

In this paper we analyzed a population of noninteracting Brownian particles moving in a common environment with stochastically gated absorption. We showed that the stochastic gating mitigated the spatial decay of the steady-state absorption density as a function of distance from the source of particles. If we interpret absorption in terms of the delivery of diffusively transported particles to targets along the dendrite or axon of a neuron, then gating provides another mechanism for synaptic democracy [22]. Similar considerations would hold if transport had an active component in the form of an advection term. One of the important consequences of a common switching environment at the population level is that there are statistical correlations in the distribution of particles with respect to different realizations of the absorbing environment. An analogous result holds for diffusion in bounded domains with stochastically gated boundary conditions [34–37] and populations of regulatory gene networks subject to the same switching environment [43,44].

One of the major simplifications of our analysis was to take the absorption rate to be spatially uniform. Although we did also consider an example of spatially heterogeneous absorption, involving N spatially localized traps, we assumed for simplicity that the traps opened and closed simultaneously (possibly due to some external drive). Although one could formulate the corresponding stochastic dynamics in the case of a population of Brownian particles diffusing in a domain with independently switching localized traps, the analysis rapidly becomes unwieldy; see also the recent study of stochastically gated gap junctions [37].

At the level of a single Brownian particle switching conformational states, one could extend the analysis in Sec. II to a variety of trapping scenarios, including higher-dimensional bounded domains with a distribution of static or dynamic traps within the domain or on the boundary of the domain. Indeed, we have previously shown how the notion of synaptic democracy extends to higher-dimensional domains with radial symmetry and reversible traps [25]. Generalizing the population level analysis of Secs. III and IV, however, requires a deeper understanding of possible mechanisms underlying the physical gating of trapping regions or inactivation domains, resulting in a common switching environment shared by all the particles. Only then can one make predictions regarding the nature of correlations induced by the switching environment.

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APPENDIX

In this appendix we extend the moment equation analysis of previous work [34] to the case of gated absorption. The first step is to spatially discretize the stochastic FP equation (3.1) and the auxiliary equation (3.2), yielding a random walk model. Introduce the lattice spacing ℓ and set $x = j\ell, \ell \in \mathbb{Z}^+$. Let $P_j(t) = P(j\ell,t)$ and $Q_j(t) = Q(j\ell,t)$. This yields the piecewise-deterministic system of ODEs

$$\frac{dP_i}{d\tau} = \Delta P_i - \gamma[1-k(t)]P_i, \quad i \geqslant 1, \tag{A1}$$

$$\frac{dQ_i}{d\tau} = \gamma[1-k(t)]P_i, \quad i \geqslant 1, \tag{A2}$$

with $Q_j(0) = 0$ and $P_j(0) = \delta_{j,1}$. Here Δ is the discrete Laplacian with

$$\Delta P_i = \frac{D}{\ell^2}[P_{i+1} + P_{i-1} - 2P_i]$$

for $i \geqslant 2$ and

$$\Delta P_1 = \frac{2D}{\ell^2}[P_2 - P_1].$$

The last equation implements the reflecting boundary condition at $x = 0$.

Let $\mathbf{P}(t) = (P_j(t), j \geqslant 1)$ and $\mathbf{Q}(t) = (Q_j(t), j \geqslant 1)$, and introduce the probability density

$$\begin{aligned}\text{Prob}\{&\mathbf{P}(t) \in (\mathbf{P},\mathbf{P}+d\mathbf{P}),\mathbf{Q}(t) \in (\mathbf{Q},\mathbf{Q}+d\mathbf{Q}),k(t)=k\}\\ &= \varrho_k(\mathbf{P},\mathbf{Q},t)d\mathbf{P}d\mathbf{Q}.\end{aligned} \tag{A3}$$

The probability density ϱ evolves according to the following infinite-dimensional CK equation:

$$\begin{aligned}\frac{\partial \varrho_k}{\partial \tau} =& -\sum_{i\geqslant 1}\frac{\partial}{\partial P_i}\{[\Delta P_i - \gamma(1-k)P_i]\varrho_k(\mathbf{P},\mathbf{Q},t)\}\\ &-\sum_{i\geqslant 1}\frac{\partial}{\partial Q_i}[\gamma(1-k)P_i\varrho_k(\mathbf{P},\mathbf{Q},t)]\\ &+\sum_{m=0,1}W_{km}\varrho_m(\mathbf{P},\mathbf{Q},\tau),\end{aligned} \tag{A4}$$

where $\mathbf{W}$ is the generator of the two-state Markov process. Since the CK equation (A4) is linear in the P_j and Q_j, it follows that we can obtain a closed set of equations for the first-order (and higher-order) moments of the density ϱ_k.

1. First-order moments

Let

$$\mathcal{P}_{k,j}(t) = \mathbb{E}[P_j(t)1_{k(t)=k}] = \int \varrho_k(\mathbf{P},\mathbf{Q},t)P_j d\mathbf{P}d\mathbf{Q}, \tag{A5}$$

and

$$\mathcal{Q}_j(t) = \mathbb{E}[Q_j(t)] = \int \varrho(\mathbf{P},\mathbf{Q},t)Q_j d\mathbf{P}d\mathbf{Q}, \tag{A6}$$

where $\varrho = \varrho_0 + \varrho_1$, and

$$\int F(\mathbf{P},\mathbf{Q})d\mathbf{P}d\mathbf{Q} = \left[\prod_j \int_0^\infty dP_j dQ_j\right] F(\mathbf{P},\mathbf{Q}).$$

Multiplying both sides of Eq. (A4) by P_j and integrating with respect to $\mathbf{P},\mathbf{Q}$ gives [after integrating by parts and assuming that $\varrho_n(\mathbf{P},\mathbf{Q},\tau) \to 0$ as $\mathbf{P},\mathbf{Q} \to \infty$]

$$\frac{d\mathcal{P}_{k,i}}{dt} = \Delta\mathcal{P}_{k,i} - \gamma(1-k)\mathcal{P}_{k,i} + \sum_{m=0,1} W_{km}\mathcal{P}_{m,i}. \tag{A7}$$

If we now set $V_k(j\ell,t) = \mathcal{P}_{k,j}(t)$ and retake the continuum limit $\ell \to 0$, we recover the first-order moment equations (3.5). Similarly, multiplying both sides of Eq. (A4) by Q_j, integrating with respect to $\mathbf{P},\mathbf{Q}$ and summing over k gives

$$\frac{d\mathcal{Q}_j}{dt} = \gamma\mathcal{P}_{0,i}. \tag{A8}$$

Therefore, setting $q(j\ell,t) = \mathcal{Q}_j(t)$ and retaking the continuum limit yields Eq. (3.7).

2. Second-order moments

We now define the second-order moments

$$C_{k,ij}(t) = \mathbb{E}[P_i(t)P_j(t)1_{k(t)=k}] = \int P_i P_j \varrho_k(\mathbf{P},\mathbf{Q},t) d\mathbf{P} d\mathbf{Q},$$

$$R_{k,ij}(t) = \mathbb{E}[P_i(t)Q_j(t)1_{k(t)=k}] = \int P_i Q_j \varrho_k(\mathbf{P},\mathbf{Q},t) d\mathbf{P} d\mathbf{Q},$$

and

$$S_{ij}(t) = \mathbb{E}[Q_i(t)Q_j(t)] = \int Q_i Q_j \varrho(\mathbf{P},\mathbf{Q},t) d\mathbf{P} d\mathbf{Q}, \quad \text{(A9)}$$

Multiplying both sides of the CK equation (A4) by $P_i(t)P_j(t)$ and integrating with respect to $\mathbf{P},\mathbf{Q}$ gives (after integration by parts)

$$\frac{dC_{k,ij}}{dt} = \Delta^{(2)} C_{k,ij} - 2\gamma(1-k)C_{k,ij} + \sum_{m=0,1} W_{km} C_{m,ij}, \quad \text{(A10)}$$

where $\Delta^{(2)}$ is the two-dimensional discrete Laplacian:

$$\Delta^{(2)} F_{ij} = \frac{D}{\ell^2}[F_{i+1,j} + F_{i-1,j} - 2F_{ij}] + \frac{D}{\ell^2}[F_{i,j+1} + F_{i,j-1} - 2F_{ij}].$$

If we now set $C_k(i\ell,j\ell,t) = C_{k,ij}(t)$ and retake the continuum limit $\ell \to 0$, we recover the second-order moment equations (3.8). As expected, these equations do not couple to moments of $Q_j(t)$. Similarly, multiplying both sides of the CK equation (A4) by either $P_i(t)Q_j(t)$ or $Q_i(t)Q_j(t)$, integrating with respect to $\mathbf{P},\mathbf{Q}$, and summing over k in the latter case gives, respectively,

$$\frac{dR_{k,ij}}{dt} = \Delta_i R_{k,ij} - \gamma(1-k)R_{k,ij} + \gamma(1-k)C_{k,ij} + \sum_{m=0,1} W_{km} R_{m,ij}$$

and

$$\frac{dS_{ij}}{dt} = \gamma(R_{0,ij} + R_{0,ji}). \quad \text{(A11)}$$

Here Δ_i indicates that the discrete Laplacian acts on the i variable. These yield Eqs. (3.12) and (3.13) in the continuum limit. (Note that, in the above derivations, we have assumed that integrating with respect to $\mathbf{P},\mathbf{Q}$ and taking the continuum limit commute. One can also avoid the issue that $\mathbf{P},\mathbf{Q}$ are infinite-dimensional vectors by carrying out the discretization over a finite domain $[0,L]$ and taking the limit $L \to \infty$ once the moment equations have been derived.)

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