SIAM J. APPL. MATH.
Vol. 80, No. 1, pp. 312–337

EFFECTIVE PERMEABILITY OF A GAP JUNCTION WITH AGE-STRUCTURED SWITCHING*

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Abstract. We analyze the diffusion equation in a bounded interval with a stochastically gated interior barrier at the center of the domain. This represents a stochastically gated gap junction linking a pair of identical cells. Previous work has modeled the switching of the gate as a two-state Markov process and used the theory of diffusion in randomly switching environments to derive an expression for the effective permeability of the gap junction. In this paper we extend the analysis of gap junction permeability to the case of a gate with age-structured switching. The latter could reflect the existence of a set of hidden internal states such that the statistics of the non-Markovian two-state model matches the statistics of a higher-dimensional Markov process. Using a combination of the method of characteristics and transform methods, we solve the partial differential equations for the expectations of the stochastic concentration, conditioned on the state of the gate and after integrating out the residence time of the age-structured process. This allows us to determine the jump discontinuity of the concentration at the gap junction and thus the effective permeability. We then use stochastic analysis to show that the solution to the stochastic PDE is a certain statistic of a single Brownian particle diffusing in a stochastically fluctuating environment. In addition to providing a simple probabilistic interpretation of the stochastic PDE, this representation enables an efficient numerical approximation of the solution of the PDE by Monte Carlo simulations of a single diffusing particle. The latter is used to establish that our analytical results match those obtained from Monte Carlo simulations for a variety of age-structured distributions.

Key words. gap junction, age-structure, non-Markovian, characteristics, stochastic processes

AMS subject classifications. 92C37, 92C30, 82C31, 35K20, 35R60

DOI. 10.1137/18M1223940

1. Introduction.

Gap junctions are intracellular gates that allow small diffusing molecules to undergo cytoplasmic transfer between adjacent cells [13, 37, 17]. Cells sharing a gap junction channel each provide a hemichannel (connexon) that connects head-to-head. Each hemichannel is composed of proteins called connexins that exist as various isoforms named Cx23 through Cx62, with Cx43 being the most common. The physiological properties of a gap junction, including its permeability and gating characteristics, are determined by the particular connexins forming the channel. Gap junctions have been found in nearly all animal organs and tissues and facilitate direct electrical and chemical signaling [10]. This signaling does not need to be confined locally, and long-range signaling via the propagation of chemicals or ions from a triggering cell can occur [11, 36, 38, 31, 32]. Gap junctions control the flow of diffusing molecules due to their restrictive geometries and via the action of voltage and chemical gates, analogous to the opening and closing of ion channels [8]. This is often modeled by taking the gap junctions to have an effective permeability. In the case of steady-state solutions, it is then possible to reduce the effects of gap junctions to a permeability-dependent rescaling of the diffusion coefficient, from which an effective diffusion coefficient can be calculated.

*Received by the editors October 31, 2018; accepted for publication (in revised form) October 31, 2019; published electronically January 30, 2020.
https://doi.org/10.1137/18M1223940

Funding: The work of the first author was supported by the National Science Foundation through grant DMS-1613048. The work of the second author was supported by the National Science Foundation through grants DMS-1814832 and DMS-RTG 1148230.

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The classical setup analyzing diffusive flow through gap junctions is the following [25]. Suppose molecules diffuse along a one-dimensional line composed of two cells connected by a gap junction (see Figure 1.1(a)). To illustrate the idea, we will not consider nonlinearities arising from chemical interactions. Compared to the cytoplasm, gap junctions have a high resistance, here modeled by an effective permeability μ. We will assume that both cells are of length L, so that the location of the gap junction is at L. In each cell, particles diffuse according to

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2}, \quad x \in (0, L) \cup (L, 2L). \tag{1.1}$$

For physiological scales within cells, the diffusion coefficient D can vary from a few $\mu\mathrm{m}^2/s$ to hundreds of $\mu\mathrm{m}^2/s$, depending on factors such as particle size and the viscosity of the media. At the intercellular boundary $x = L$, the concentration is discontinuous due to the permeability. Conservation of the diffusive flux allows us to write down interior boundary conditions at each gap junction

$$-D\frac{\partial u(L^-, t)}{\partial x} = -D\frac{\partial u(L^+, t)}{\partial x} = \mu[u(L^-, t) - u(L^+, t)]. \tag{1.2}$$

It should be noted that only the first equality is conservation of flux. The second equality is the choice for the form of the flux through the gap junction, in our case based on the difference in concentration at the interior boundary. Here the parameter μ is a measure of the velocity for the particles moving through the gap junction based on the difference in concentration on either side, and as such has units of length per time. To have a well-posed problem, we also need exterior boundary conditions at $x = 0$ and $x = 2L$. For concreteness, we assume that there are concentration reservoirs at both ends and impose the Dirichlet boundary conditions

$$u(0, t) = 0, \quad u(2L, t) = \eta, \tag{1.3}$$

where η is the exterior concentration at the right boundary and, without loss of generality, we have set the exterior concentration at the left boundary to zero. This is valid since the same boundary conditions used here can be obtained by shifting the density u to be 0 at $x = 0$ without changing (1.1), (1.2). While other boundary conditions may be considered, the current choice greatly simplifies the analysis in later sections.

In steady-state, there is a constant flux $J_0 = -DK_0$, and the density within each cell is given by a linear function with slope K_0. Enforcing the external boundary condition at $x = 0$ and interior boundary conditions at $x = L$, we find that

$$u(x) = \begin{cases} K_0 x, & x \in (0, L), \\ K_0 x + U, & x \in (L, 2L), \end{cases} \tag{1.4}$$

where $U = u(L^+) - u(L^-)$ is the change in density across the cellular gate. This gives two unknowns to solve for: K_0 and U. By enforcing the exterior boundary condition at $x = 2L$ we arrive at $\eta = 2K_0L + U$. Since $J_0 = \mu[u(L^-) - u(L^+)] = -\mu U$, it follows that $U = DK_0/\mu$ and thus $\eta = 2K_0L + DK_0/\mu$. The latter equation can be solved for K_0, which establishes that the steady-state diffusive flux is

$$J_0 = -\frac{D\eta}{2L}\left[1 + \frac{D}{2\mu L}\right]^{-1}. \tag{1.5}$$

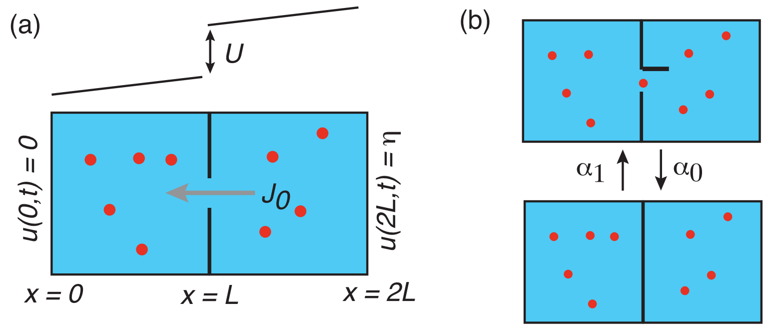

FIG. 1.1. *Pair of cells, each of length L, connected internally by a gap junction.* (a) *Static gap junction with permeability μ. In steady-state, there is a constant flux J_0 through the system, but there is a jump discontinuity of size U at the gap junction.* (b) *Dynamic gap junction that stochastically switches between open and closed states with transition rates $\alpha_{0,1}$. In the open state particles pass through the gap junction freely.*

Defining an effective diffusion coefficient $D_e = -J_0(2L/\eta)$, we see that the reciprocal can be expressed more succinctly as

$$\frac{1}{D_e} = \frac{1}{D} + \frac{1}{2\mu L}. \tag{1.6}$$

In the above model, the permeability μ of the gap junction is introduced as a model parameter, rather than being derived from first principles. Recently, we developed one approach to deriving an effective permeability, in which a gap junction randomly switches between an open and a closed state due to thermal fluctuations [5] (see Figure 1.1(b)). This could be due to a physical gate at the gap junction, which only allows the passage of molecules when it is open. More specifically, suppose that there is a discrete random variable $n(t) \in \{0, 1\}$ such that the gap junction is open when $n(t) = 0$ and closed when $n(t) = 1$.[1] We will assume that transitions between the two states $n = 0, 1$ are described by the two-state Markov process

$$0 \underset{\alpha_1}{\overset{\alpha_0}{\rightleftharpoons}} 1.$$

Analogous to stochastically gated neuronal ion channels [2], these switching rates could depend on the local voltage of the cell in the case of a voltage-gated gap junction or the local concentration of the diffusing signaling molecule in the case of a chemically gated gap junction. In the latter case, this would lead to a nontrivial coupling between the switching process and diffusion. For analytical tractability, we assume that the random switching of the gate is independent of the diffusion process, which would hold for a voltage-gated gap junction in which the voltage dynamics evolves on a slower time-scale than stochastic switching and diffusion.

[1] In our previous work, we also determined the permeability of a one-dimensional array of N gap junctions under the simplifying assumption that all gap junctions open and close together. The case of N independently switching gap junctions is much more complicated, since one has to assign a discrete random variable $n_k(t) \in \{0, 1\}$ to each gate so that the resulting Markov chain is of size 2^N. The reduced model of simultaneously switching gates provides an upper bound to the effective permeability and can also be used to model multiple diffusing molecules independently switching between different conformational states, only one of which allows them to traverse a gap junction [5].

The random opening and closing of the gap junction means that the boundary conditions (1.2) of the classical model have to be replaced by the stochastic boundary conditions

$$u(L^-,t) = u(L^+,t), \quad \partial_x u(L^-,t) = \partial_x u(L^+,t) \text{ for } n(t) = 0, \tag{1.7a}$$

$$\partial_x u(L^-,t) = 0 \quad \partial_x u(L^+,t) = 0 \text{ for } n(t) = 1. \tag{1.7b}$$

That is, when the gap junction is open, there is continuity of the concentration and the flux across $x = L$, whereas when the gap junction is closed, the right-hand boundary of the first cell and the left-hand boundary of the second cell are reflecting. The effective permeability of the gap junction can be obtained by introducing the first-order moments

$$V_n(x,t) = \mathbb{E}[u(x,t)1_{n(t)=n}],$$

where expectation is taken with respect to realizations of the discrete stochastic process $n(t)$, and $1_{n(t)=n} = 1$ if $n(t) = n$ and is zero otherwise. Setting $V(x,t) = V_0(x,t) + V_1(x,t)$, one finds that $V(x) = \lim_{t\to\infty} V(x,t)$ satisfies the same steady-state equations (1.4). However, in order to determine the constant slope K_0, and hence the effective flux J_0, it is necessary to solve the boundary value problems for the individual components $V_n(x)$. The final result is that the effective permeability μ_e in the case of two cells with a single stochastically gated gap junction satisfies [5]

$$\frac{1}{\mu_e} = \frac{2\rho_1}{\rho_0}\frac{\tanh(\xi L)}{\xi D}, \tag{1.8}$$

where

$$\xi = \sqrt{(\alpha_0+\alpha_1)/D}, \quad \rho \equiv \begin{pmatrix} \rho_0 \\ \rho_1 \end{pmatrix} = \frac{1}{\alpha_0+\alpha_1}\begin{pmatrix} \alpha_1 \\ \alpha_0 \end{pmatrix}. \tag{1.9}$$

The dependence of μ_e on L comes from the fact that the particle source is located at L and that our effective permeability is essentially a measure of velocity, which must include the effects of diffusion-driven transport over the adjoining distance. Since $0 < \tanh(\xi L) < 1$, this transportation effect increases the effective permeability, an effect that disappears for $\xi L \gg 1$. We conjecture that a similar phenomenon would hold for a more general two-dimensional domain, provided that there is an external source of particles at the boundary opposite the gate.

In this paper we extend the analysis of gap junction permeability [5] by adapting our recent work on one-dimensional diffusion in domains with age-structured switching boundaries [7]. Age-structured models are probably best known within the context of birth-death processes in population biology, where the birth and death rates depend on the age of the underlying populations [33, 40, 9, 19]. These could be cells undergoing differentiation or proliferation [41, 39, 35] or whole organisms undergoing reproduction [26]. There are also a growing number of applications of age-structured models within cell biology, including cell motility [14, 15] and microtubule catastrophes [21]. In the latter case, experimental evidence suggests that the rate at which a microtubule switches from a growth phase to a shrinkage phase (catastrophe rate) increases with the age of the microtubule. Diffusion in age-structured switching environments can be motivated as follows. The gating dynamics of protein-based channels is often governed by transitions between conformational states in a very complex potential landscape, reflecting the intrinsic multidimensionality of the problem. This can result in local residence times that are nonexponential, as measured using patch clamp experiments [18]. One way to model this is to treat the system as having a large number of conformational states with exponential transition rates between each. Since most observed nonexponential distributions can be approximated by a finite sum of exponentials, this can then be used to fit the data. One is essentially lifting from a low-dimensional non-Markovian state space to a high-dimensional Markovian one. The drawback is that the number of states needed to fit the data changes, depending on the conditions, such as temperature, under which the data is obtained. One workaround is to use an age structured model that only incorporates two states, the open and close states, and whose first passage time statistics from the open state to the closed state, or vice versa, match that of the original process.

Finally, note that for simplicity we restrict our analysis to one-dimensional domains. However, biological cells that communicate via gap junctions are typically spherically shaped such that the gap junctions are small holes relative to the size of cells. This adds another major level of complexity, beyond dealing with higher-dimensional characteristics, since it is necessary to introduce a boundary layer in the neighborhood of each junction in order to deal with the singular nature of Green's functions in higher dimensions, which is known as the narrow escape problem [20]. Previous work has analyzed diffusion in higher-dimensional domains with stochastically gated small holes in the boundary, but without any age structure [34, 4]. An alternative approach would be to carry out an effective homogenization of the medium, along lines analogous to nonswitching gap junctions [25].

2. Single gap junction with age-structured switching. Let us again consider a pair of cells of size L connected by a gap junction at $x = L$ that stochastically switches between an open state and a closed state, denoted by $n = 0$ and $n = 1$, respectively (see Figure 1.1(b)). Now, however, the switching rates are taken to depend on the residence time τ that the gap junction has been in the current state. This generates a non-Markovian chain for the state of each gate given by

$$0 \underset{\alpha_1(\tau)}{\overset{\alpha_0(\tau)}{\rightleftharpoons}} 1,$$

where we restrict $\alpha_n(\tau)$ so that the expected time for the gate to change state is finite. The resulting diffusion equation takes the form (1.1) with exterior boundary conditions (1.3) and state-dependent interior boundary conditions at the gap junction given by (1.7). A key point that we will use later is that the discrete process is non-Markovian only if the state of the gate given by $n(t)$ is being tracked. The probability of the gate changing states depends on both n and the residence time τ. If we also keep track of the history by tracking τ, the process $(n(t), \tau(t))$ is Markovian as the probability of a transition happening in the next infinitesimal time interval $[t, t + dt]$ is now only dependent on information at time t.

Let $\Lambda_n(t, \tau)$ denote the probability density that $n(t) = n$, and $\tau(t) = \tau$, where $\tau(t)$ is the time elapsed since the last transition. The corresponding age-structured master equation for Λ_n is

$$\frac{\partial \Lambda_0(t,\tau)}{\partial t} + \frac{\partial \Lambda_0(t,\tau)}{\partial \tau} = -\alpha_0(\tau)\Lambda_0(t,\tau), \tag{2.1a}$$

$$\frac{\partial \Lambda_1(t,\tau)}{\partial t} + \frac{\partial \Lambda_1(t,\tau)}{\partial \tau} = -\alpha_1(\tau)\Lambda_1(t,\tau), \tag{2.1b}$$

which is supplemented by the boundary conditions

$$\Lambda_0(t,0) = \int_0^\infty \alpha_1(\tau)\Lambda_1(t,\tau)d\tau, \quad \Lambda_1(t,0) = \int_0^\infty \alpha_0(\tau)\Lambda_0(t,\tau)d\tau, \tag{2.1c}$$

and the initial conditions $\Lambda_n(0,\tau) = p_n(\tau)$ with $\sum_{n=0,1}\int_0^\infty p_n(\tau)d\tau = 1$. The upper limit ∞ in (2.1c) is greater than the time t in order to capture any transitions from a state where the age of the gate τ was positive at $t = 0$. Finally, the marginal distribution $\lambda_n(t)$ is obtained by integrating with respect to τ:

$$\lambda_n(t) = \int_0^\infty \Lambda_n(t,\tau)d\tau. \tag{2.2}$$

Note that $\lambda_n(t)$ is the probability that the system is in state n at time t and thus $\lambda_0(t) + \lambda_1(t) = 1$ for all t.

Since the randomly switching boundary conditions make the formerly deterministic variable u into a random variable, we will analyze its behavior by looking at moment equations. As previously mentioned, the process (n,τ) is Markovian as the history of the gate is being tracked through τ, so we will first introduce the τ-dependent first-order moments V_n with

$$V_n(x,t,\tau)\,d\tau = \mathbb{E}[u(x,t)1_{\{n(t)=n\}\cup\{\tau<\tau(t)<\tau+d\tau\}}]. \tag{2.3}$$

As in the case without age structure, this expectation is taken with respect to realizations of the discrete stochastic process $n(t)$, but we have extended this by also conditioning on a particular residence time $\tau(t)$ for the age of the state $n(t)$. In particular $1_{\{n(t)=n\}\cup\{\tau<\tau(t)<\tau+d\tau\}} = 1$ if $n(t) = n$ and $\tau(t) \in (\tau, \tau + d\tau)$, and is zero otherwise. That is, V_n satisfies

$$\mathbb{E}[u(x,t)1_{\{n(t)=n\}\cup\{\tau(t)\in A\}}] = \int_A V_n(x,t,\tau)\,d\tau$$

for subsets $A \subset [0,\infty)$. Assuming the density Λ_n exists, the Radon–Nikodym theorem guarantees the existence and uniqueness of V_n. Extending our previous work on diffusion in switching environments [3, 28, 7], the following system of equations for $V_n(x,t,\tau)$ can be derived:

$$\frac{\partial V_n}{\partial t} + \frac{\partial V_n}{\partial \tau} = D\frac{\partial^2 V_n}{\partial x^2} - \alpha_n(\tau)V_n(x,t,\tau), \quad x \in (0,L)\cup(L,2L) \tag{2.4}$$

with exterior boundary conditions

$$V_n(0,t,\tau) = 0, \quad V_n(2L,t,\tau) = \Lambda_n(t,\tau)\eta \tag{2.5a}$$

and interior boundary conditions

$$V_0(L^-,t,\tau) = V_0(L^+,t,\tau), \quad \partial_x V_0(L^-,t,\tau) = \partial_x V_0(L^+,t,\tau), \tag{2.5b}$$

$$\partial_x V_1(L^-,t,\tau) = 0, \quad \partial_x V_1(L^+,t,\tau) = 0. \tag{2.5c}$$

The boundary conditions for τ are given by

$$V_0(x,t,0) = N_1(x,t), \quad V_1(x,t,0) = N_0(x,t) \tag{2.6}$$

with

$$N_n(x,t) := \int_0^\infty \alpha_n(\tau) V_n(x,t,\tau) d\tau, \tag{2.7}$$

and the initial conditions at $t = 0$ are

$$V_n(x,0,\tau) = V_n^{(0)}(x) p_n(\tau) \tag{2.8}$$

for some initial spatial distribution $V_n^{(0)}(x)$. For a full derivation of (2.4) with similar boundary conditions, we refer readers to [7]. The key idea is to discretize space, formulate the probabilistic problem for the system of discretized equations, and then retake the continuum limit to arrive at (2.4).

In order to derive a formula for the effective permeability of the gap junction, we need to determine the τ-independent moments

$$M_n(x,t) \equiv \int_0^\infty V_n(x,t,\tau) d\tau = \mathbb{E}[u(x,t) 1_{n(t)=n}], \tag{2.9}$$

which evolve according to a non-Markovian master equation. We can find the general form of the master equation in a fairly straightforward manner [7]. Integrating (2.4) from $\tau = 0$ to $\tau = \infty$, interchanging differentiation with integration, and using the fundamental theorem of calculus yields

$$\frac{\partial M_n(x,t)}{\partial t} + V_n(x,t,\infty) - V_n(x,t,0) = D \frac{\partial^2 M_n(x,t)}{\partial x^2} - \int_0^\infty \alpha_n(\tau) V_n(x,t,\tau) d\tau.$$

Using the boundary condition (2.6) and the fact that $V_n(x,t,\tau) \to 0$ as $\tau \to \infty$ since the expected switching time is finite, we obtain

$$\frac{\partial M_n(x,t)}{\partial t} = D \frac{\partial^2 M_n(x,t)}{\partial x^2} - N_n(x,t) + N_{1-n}(x,t), \quad x \in (0,L) \cup (L,2L) \tag{2.10}$$

with boundary conditions

$$M_n(0,t) = 0, \quad M_n(2L,t) = \eta \lambda_n(t), \tag{2.11a}$$

$$M_0(L^-,t) = M_0(L^+,t), \quad \partial_x M_0(L^-,t) = \partial_x M_0(L^+,t), \tag{2.11b}$$

$$\partial_x M_1(L^-,t) = 0 = \partial_x M_1(L^+,t). \tag{2.11c}$$

We are ultimately interested in the steady-state solution

$$M(x) = \lim_{t\to\infty} [M_0(x,t) + M_1(x,t)], \tag{2.12}$$

under the assumption that the following limits exist:

$$\lambda_n^* = \lim_{t\to\infty} \lambda_n(t) \tag{2.13}$$

with $\lambda_0^* + \lambda_1^* = 1$. Adding the steady-state versions of (2.10) for $M_0(x)$ and $M_1(x)$ gives

$$D \frac{d^2 M(x)}{dx^2} = 0, \quad x \in (0,L) \cup (L,2L), \tag{2.14}$$

with $M(0) = 0$ and $M(2L) = \eta$, which indicates that $M(x)$ is the piecewise linear function

$$M(x) = \begin{cases} K_0 x, & x \in [0, L), \\ K_0(x - 2L) + \eta, & x \in (L, 2L]. \end{cases} \tag{2.15}$$

Given the slope K_0, we can determine the effective permeability by setting $J_0 = -K_0/D$ and comparing with (1.5). However, in order to determine K_0, it is necessary to impose the interior boundary conditions (2.11b), (2.11c) at $x = L$, which involve the components $M_n(x)$ rather than $M(x)$. This means that we have to solve equations (2.10) directly, and thus deal with the fact that the integral terms N_n are currently expressed in terms of V_n, rather that M_n. In order to rewrite N_n in terms of M_n, and to solve the resulting equation for M_n, we will make use of transform techniques. Since the analysis is rather involved, it is useful first to review the calculation of $\lambda_n(t)$ [14, 7]. Moreover, we need the expressions for λ_n^* in order to specify the steady-state boundary conditions (2.11a). One exception is the symmetric case $\alpha_0(\tau) = \alpha_1(\tau)$, for which $\lambda_0^* = \lambda_1^* = 1/2$.

2.1. Calculation of $\boldsymbol{\lambda_n(t)}$. The first step is to introduce the complementary functions

$$r_n(t) = \int_0^\infty \alpha_n(\tau)\Lambda_n(t,\tau)d\tau \tag{2.16}$$

for $n = 0, 1$. We then decompose the right-hand sides of (2.2) and (2.16) in order to distinguish between switching events that occur due to nonzero age at $t = 0$ and switching events for which $\tau < t$:

$$\lambda_n(t) = \int_0^t \Lambda_n(t,\tau)d\tau + \int_t^\infty \Lambda_n(t,\tau)d\tau, \tag{2.17a}$$

$$r_n(t) = \int_0^t \alpha_n(\tau)\Lambda_n(t,\tau)d\tau + \int_t^\infty \alpha_n(\tau)\Lambda_n(t,\tau)d\tau. \tag{2.17b}$$

The hyperbolic equations (2.1a) and (2.1b) can be solved using the method of characteristics:

$$\Lambda_n(t,\tau) = \Lambda_n(t-\tau, 0)W_n(\tau) \quad \text{if} \quad t > \tau, \tag{2.18a}$$

$$\Lambda_n(t,\tau) = \Lambda_n(0, \tau - t)\frac{W_n(\tau)}{W_n(t-\tau)} \quad \text{if} \quad t \le \tau, \tag{2.18b}$$

where

$$W_n(\tau) \equiv \mathrm{e}^{-\int_0^\tau \alpha_n(t')dt'} \tag{2.19}$$

is the survival probability that the system has not switched after residing in state n for time τ. Substituting the solutions (2.18a) and (2.18b) into (2.17) and imposing the initial conditions $\Lambda_n(0,\tau) = p_n(\tau)$ shows that

$$\lambda_n(t) = (r_{1-n} * W_n)(t) + H_n(t), \tag{2.20a}$$

$$r_n(t) = (r_{1-n} * \omega_n)(t) + h_n(t) \tag{2.20b}$$

with $(f * g)(t) := \int_0^t f(t-\tau)g(\tau)d\tau$. We have used (2.1c) and set

$$\omega_n(\tau) := -\frac{dW_n(\tau)}{d\tau} = \alpha_n(\tau)e^{-\int_0^\tau \alpha_n(t')dt'} \tag{2.21}$$

in addition to defining the functions

$$H_n(t) = \int_t^\infty p_n(\tau - t)\frac{W_n(\tau)}{W_n(\tau - t)}d\tau = \int_0^\infty p_n(\tau)\frac{W_n(\tau + t)}{W_n(\tau)}d\tau, \tag{2.22}$$

$$h_n(t) = \int_t^\infty p_n(\tau - t)\frac{\omega_n(\tau)}{W_n(\tau - t)}d\tau = \int_0^\infty p_n(\tau)\frac{\omega_n(\tau + t)}{W_n(\tau)}d\tau \tag{2.23}$$

that together describe the evolution of the initial conditions. It is key to note that $H_n(0) = \lambda_n(0)$, $-\frac{dH_n(t)}{dt} = h_n(t)$. Additionally, $H, h \to 0$ as $t \to \infty$, indicating that the initial data is forgotten in the large-time limit.

The next step is to Laplace transform the convolution equations (2.20a) and (2.20b), which yields

$$\widetilde{\lambda}_n(s) = \widetilde{r}_{1-n}(s)\widetilde{W}_n(s) + \widetilde{H}_n(s), \tag{2.24a}$$

$$\widetilde{r}_n(s) = \widetilde{r}_{1-n}(s)\widetilde{\omega}_n(s) + \widetilde{h}_n(s). \tag{2.24b}$$

After some algebra, and using the fact that $\widetilde{\omega}_n(s) = -s\widetilde{W}_n(s) + 1$, $\widetilde{h}_n(s) = -s\widetilde{H}_n(s) + H_n(0) = -s\widetilde{H}_n(s) + \lambda_n(0)$, we arrive at the matrix equation [7]

$$\begin{pmatrix} s + \frac{\widetilde{\omega}_0(s)}{\widetilde{W}_0(s)} & -\frac{\widetilde{\omega}_1(s)}{\widetilde{W}_1(s)} \\ -\frac{\widetilde{\omega}_0(s)}{\widetilde{W}_0(s)} & s + \frac{\widetilde{\omega}_1(s)}{\widetilde{W}_1(s)} \end{pmatrix} \begin{pmatrix} \widetilde{\lambda}_0(s) \\ \widetilde{\lambda}_1(s) \end{pmatrix} = \begin{pmatrix} \lambda_0(0) \\ \lambda_1(0) \end{pmatrix}. \tag{2.25}$$

We can now invert this equation and use the final value theorem of Laplace transforms, which states that if $\lim_{t\to\infty} f(t)$ exists, then

$$\lim_{s\to 0^+} sF(s) = \lim_{t\to\infty} f(t). \tag{2.26}$$

This yields the solution

$$\lim_{t\to\infty} \begin{pmatrix} \lambda_0(t) \\ \lambda_1(t) \end{pmatrix} = \lim_{s\to 0^+} \begin{pmatrix} s\widetilde{\lambda}_0(s) \\ s\widetilde{\lambda}_1(s) \end{pmatrix} = \frac{1}{a_\lambda + b_\lambda} \begin{pmatrix} a_\lambda & a_\lambda \\ b_\lambda & b_\lambda \end{pmatrix} \begin{pmatrix} \lambda_0(0) \\ \lambda_1(0) \end{pmatrix} = \begin{pmatrix} \frac{a_\lambda}{a_\lambda + b_\lambda} \\ \frac{b_\lambda}{a_\lambda + b_\lambda} \end{pmatrix} \tag{2.27}$$

independent of the initial data, where we have used $\lambda_0(0) + \lambda_1(0) = 1$ and defined

$$a_\lambda = \lim_{s\to 0^+} \frac{\widetilde{\omega}_1(s)}{\widetilde{W}_1(s)} = \frac{1}{\int_0^\infty W_1(t)dt}, \tag{2.28a}$$

$$b_\lambda = \lim_{s\to 0^+} \frac{\widetilde{\omega}_0(s)}{\widetilde{W}_0(s)} = \frac{1}{\int_0^\infty W_0(t)dt}. \tag{2.28b}$$

The last equalities follow assuming we have a holding time distribution with a finite first moment and that the distribution of switching times is nonarithmetic. In other words, if T_n is the stochastic time spent in state n, we need $\mathbb{E}[T_n] < \infty$, and the distribution of $(T_1, T_2, \dots)$ is not supported on a set $\{t_i | t_{i+1} = t_i + d\}$ for some constant d. This is a well known result from alternating renewal process theory [1], which states that

$$\lim_{t\to\infty} \mathbb{P}(n(t) = 1) = \frac{\mathbb{E}[T_1]}{\mathbb{E}[T_0] + \mathbb{E}[T_1]} \tag{2.29}$$

with an identical statement holding true with 0 and 1 switched. Since $\widetilde{W}_n(0) =$

$\int_0^\infty W_n(t)dt = \mathbb{E}[T_n]$, this is the same as our result. The reason we have gone through the above calculation is that it sets the groundwork and mathematical techniques for solving the equations governing the unstructured moments $M_n(x,t)$.

Finally, note that in the Markovian case, in which $\alpha_n(\tau) = \alpha_n$ for all $\tau \geq 0$, we have $\mathcal{L}\{W(t)\} = \mathcal{L}\{e^{-\alpha_n t}\} = (s+\alpha_n)^{-1}$, so that $a_\lambda = \alpha_1$, $b_\lambda = \alpha_0$.

2.2. Calculation of $N_n(x,t)$ on $[0,L)$. Consider the boundary-value problem

$$\frac{\partial M_n(x,t)}{\partial t} = D\frac{\partial^2 M_n(x,t)}{\partial x^2} - N_n(x,t) + N_{1-n}(x,t), \quad x \in (0,L), \tag{2.30}$$

with boundary conditions

$$M_n(0,t) = 0, \quad M_0(L,t) = F_0(t), \quad \partial_x M_1(L,t) = 0, \tag{2.31a}$$

where $F_0(t)$ is some unknown function. We will use a combination of transform methods and the method of characteristics to express the functions $N_n(x,t)$ in terms of $M_n(x,t)$ so that (2.30) forms a closed system of equations. This will then allow us to solve for the steady-state solutions $M_n(x)$ in terms of the steady-state value $F_0^* = \lim_{t\to\infty} F_0(t)$. Finally, the latter will be determined by solving an analogous boundary-value problem in the domain $(L,2L]$ and imposing the matching boundary conditions (2.11b) (see section 2.4). Note that in our previous work [7], we solved a simpler problem in which $F_0(t)$ was a known constant and we did not have to deal with any matching conditions. Nevertheless, the first part of the analysis proceeds along identical lines to [7], so we will only sketch the basic steps.

We begin by Fourier transforming the moment equations (2.4). In order to ensure that V_0, V_1, and $V = V_0 + V_1$ all lie in the same Fourier space, we take them to be periodic functions on the domain $[0,L]$, and then extend them to odd periodic functions on $[-L,L]$ in order to simplify the Fourier representation to just a sine series. These periodic functions will be discontinuous at $x = \pm L$. Therefore, we introduce the sine series

$$V_n(x,t,\tau) = \sum_{l=1}^{\infty} \widehat{V}_{n,l}(t,\tau)\sin(l\pi x/L), \quad n = 0,1, \tag{2.32}$$

with

$$\widehat{V}_{n,l}(t,\tau) = \frac{1}{L}\int_{-L}^{L} V_n(x,t,\tau)\sin(l\pi x/L)dx. \tag{2.33}$$

Fourier transforming equation (2.4) then gives

$$\frac{\partial \widehat{V}_{n,l}}{\partial t} + \frac{\partial \widehat{V}_{n,l}}{\partial \tau} = -\left[Dk_l^2 + \alpha_n(\tau)\right]\widehat{V}_{n,l} + \frac{2Dk_l}{L}(-1)^{l+1}V_n(L,t,\tau). \tag{2.34}$$

where $k_l = l\pi/L$. We have used the fact that the sine transform of second derivatives picks up a boundary term. We also have the initial conditions

$$\widehat{V}_{n,l}(0,\tau) = \widehat{V}_{n,l}^{(0)} p_n(\tau), \tag{2.35a}$$

$$\widehat{V}_{1-n,l}(t,0) = \int_0^\infty \alpha_n(\tau)\widehat{V}_{n,l}(t,\tau)d\tau = \mathcal{N}_{n,l}(t), \quad n = 0,1. \tag{2.35b}$$

Here $\mathcal{M}_{n,l}(t)$ and $\mathcal{N}_{n,l}(t)$ denote the sine transforms of $M_n(x,t)$ and $N_n(x,t)$. For the moment, we leave the boundary conditions for $V_n(L,t,\tau)$ unspecified.

The method of characteristics can now be used to find a solution along analogous lines to the analysis of $\Lambda_n(t,\tau)$ [7]. For $t>\tau$, we have

$$\widehat{V}_{n,l}(t,\tau) = \widehat{V}_{n,l}(t-\tau,0)W_n(\tau)e^{-Dk_l^2\tau} + B_{n,l}(t,\tau), \tag{2.36}$$

where

$$B_{n,l}(t,\tau) = W_n(\tau)e^{-Dk_l^2\tau}\frac{2Dk_l}{L}(-1)^{l+1}\int_0^\tau \frac{e^{Dk_l^2\tau'}}{W_n(\tau')}V_n(L,t-\tau+\tau',\tau')d\tau'. \tag{2.37}$$

Similarly, for $t\le\tau$ we have

$$\widehat{V}_{n,l}(t,\tau) = \widehat{V}_{n,l}(0,\tau-t)\frac{W_n(\tau)}{W_n(\tau-t)}e^{-Dk_l^2 t} + C_{n,l}(t,\tau), \tag{2.38}$$

where

$$C_{n,l}(t,\tau) = W_n(\tau)e^{-Dk_l^2 t}\frac{2k_l D}{L}(-1)^{l+1}\int_0^t \frac{\mathrm{e}^{Dk_l^2 t'}}{W_n(\tau-t+t')}V_n(L,t',\tau-t+t')dt'. \tag{2.39}$$

The functions $B_{n,l}(t,\tau)$ and $C_{n,l}(t,\tau)$ are specified in terms of the boundary conditions for $V_n(L,t,\tau)$. The next step is to decompose the right-hand sides of (2.7) and (2.9) into two parts, one of which contains the propagation of the initial data. After Fourier transforming we have

$$\mathcal{M}_{n,l}(t) = \int_0^t \widehat{V}_{n,l}(t,\tau)d\tau + \int_t^\infty \widehat{V}_{n,l}(t,\tau)d\tau,$$
$$\mathcal{N}_{n,l}(t) = \int_0^t \alpha_n(\tau)\widehat{V}_{n,l}(t,\tau)d\tau + \int_t^\infty \alpha_n(\tau)\widehat{V}_{n,l}(t,\tau)d\tau.$$

Substituting the characteristic solution into this pair of equations and using (2.35a)–(2.35b) yields

$$\mathcal{M}_{n,l}(t) = (\mathcal{N}_{1-n,l}*\Phi_{n,l})(t) + \widehat{V}_{n,l}^{(0)}\mathrm{e}^{-Dk_l^2 t}H_n(t) + R_{n,l}(t), \tag{2.40a}$$

$$\mathcal{N}_{n,l}(t) = (\mathcal{N}_{1-n,l}*\phi_{n,l})(t) + \widehat{V}_{n,l}^{(0)}\mathrm{e}^{-Dk_l^2 t}h_n(t) + S_{n,l}(t), \tag{2.40b}$$

where

$$R_{n,l}(t) = \int_0^t B_{n,l}(t,\tau)d\tau + \int_t^\infty C_{n,l}(t,\tau)d\tau, \tag{2.41a}$$

$$S_{n,l}(t) = \int_0^t \alpha_n(\tau)B_{n,l}(t,\tau)d\tau + \int_t^\infty \alpha_n(\tau)C_{n,l}(t,\tau)d\tau. \tag{2.41b}$$

$\mathcal{M}_{n,l}$ and $\mathcal{N}_{n,l}$ are analogous to λ_n and r_n from the previous section. $R_{n,l}$ and $S_{n,l}$ do not have analogues and describe the propagation of the unknown interior boundary data at $x=L$ along characteristics in Fourier space. It is also again worth mentioning that $\mathcal{M}_{n,l}(0)=\widehat{V}_{n,l}^{(0)}H_n(0)$ is the initial data for the Fourier coefficients of the first conditional moments M_n.

Analogous to the calculation of $\lambda_n(t)$, we now apply Laplace transforms to (2.40), which leads to the following algebraic system:

$$\widetilde{\mathcal{M}}_{n,l}(s) = \widetilde{\mathcal{N}}_{1-n,l}(s)\widetilde{W}_n(s+Dk_l^2) + \widehat{V}_{n,l}^{(0)}\widetilde{H}_n(s+Dk_l^2) + \widetilde{R}_{n,l}(s), \tag{2.42a}$$

$$\widetilde{\mathcal{N}}_{n,l}(s) = \widetilde{\mathcal{N}}_{1-n,l}(s)\widetilde{\omega}_n(s+Dk_l^2) + \widehat{V}_{n,l}^{(0)}\widetilde{h}_n(s+Dk_l^2) + \widetilde{S}_{n,l}(s). \tag{2.42b}$$

Solving (2.42a) for $\widetilde{\mathcal{N}}_{1-n,l}(s)$ and combining this with (2.42b) gives [7]

$$\widetilde{\mathcal{N}}_{n,l}(s) = \frac{\widetilde{\omega}_n(s+Dk_l^2)}{\widetilde{W}_n(s+Dk_l^2)}\left[\widetilde{\mathcal{M}}_{n,l}(s) - \widetilde{R}_{n,l}(s)\right] - \widehat{V}_{n,l}^{(0)}\frac{\widetilde{H}_n(s+Dk_l^2)}{\widetilde{W}_n(s+Dk_l^2)} + \widehat{V}_{n,l}^{(0)}H_n(0) + \widetilde{S}_{n,l}(s). \tag{2.43}$$

Equation (2.43) thus determines the Fourier–Laplace transform of $N_n(x,t)$ in terms of the corresponding transform of $M_n(x,t)$ and the boundary conditions at $x = L$. Moreover, after some algebra it can be shown that [7]

$$s\widetilde{\mathcal{M}}_{n,l}(s) - \mathcal{M}_{n,l}(0) = -Dk_l^2\widetilde{\mathcal{M}}_{n,l}(s) + \widetilde{\mathcal{N}}_{1-n,l}(s) - \widetilde{\mathcal{N}}_{n,l}(s) + [Dk_l^2 + s]\widetilde{R}_{n,l}(s) + \widetilde{S}_{n,l}(s). \tag{2.44}$$

The inverse Fourier–Laplace transform of (2.44) recovers (2.10) with the boundary conditions

$$M_n(0,t) = 0, \quad M_n(L,t) = F_n(t) \tag{2.45}$$

with

$$\frac{2Dk_l}{L}(-1)^{l+1}\widetilde{\mathcal{F}}_n(s) = [Dk_l^2 + s]\widetilde{R}_{n,l}(s) + \widetilde{S}_{n,l}(s). \tag{2.46}$$

One final condition is needed so that $\widetilde{R}_{n,l}(s)$ and $\widetilde{S}_{n,l}(s)$ can be uniquely expressed in terms of $\widetilde{\mathcal{F}}_n(s)$. Following [7], we take

$$\widetilde{R}_{n,l}(s) = \frac{2}{Lk_l}(-1)^{l+1}\widetilde{\mathcal{F}}_n(s)\left[1 - \frac{\widetilde{W}_n(s+Dk_l^2)}{\widetilde{W}_n(s)}\right], \tag{2.47}$$

which yields the correct result when $u(L,t) = \eta$ and hence $V_n(L,t,\tau) = \eta\Lambda_n(t,\tau)$.

2.3. Steady-state analysis. Suppose that the following limits exist:

$$N_n(x) = \lim_{t\to\infty} N_n(x,t), \quad F_n^* = \lim_{t\to\infty} F_n^*(t).$$

The steady-state version of (2.10) takes the form

$$0 = D\frac{d^2M_n(x)}{\partial x^2} - N_n(x) + N_{1-n}(x) \tag{2.48}$$

with boundary conditions

$$M_n(0) = 0, \quad M_0(L) = F_0^*, \quad \partial_x M_1(L) = 0. \tag{2.49}$$

For the moment, rather than imposing the Neumann boundary condition, we take $M_1(L) = F_1^*$. In Fourier space, we have

$$0 = -Dk_l^2\mathcal{M}_{n,l} + \mathcal{N}_{1-n,l} - \mathcal{N}_{n,l} + \frac{2Dk_l}{L}(-1)^{l+1}F_n^*, \tag{2.50}$$

where now $\mathcal{M}_{n,l}$ and $\mathcal{N}_{n,l}$ are the constant Fourier coefficients of the steady-state solutions. In order to determine the Fourier coefficients $\mathcal{N}_{n,l}$, we apply the final value theorem of Laplace transforms to (2.43), (2.46), and (2.47) and then rewrite (2.43) in terms of $\mathcal{M}_{n,l}$ and F_n^*:

$$\mathcal{N}_{n,l} = \frac{\widetilde{\omega}_n(Dk_l^2)}{\widetilde{W}_n(Dk_l^2)}\mathcal{M}_{n,l} + \frac{2}{Lk_l}(-1)^{l+1}F_n^*\left[\frac{1}{\widetilde{W}_n(0)} - \frac{\widetilde{\omega}_n(Dk_l^2)}{\widetilde{W}_n(Dk_l^2)}\right]. \tag{2.51}$$

Combined with the fact that $M_n(x) = M(x) - M_{1-n}(x)$, we can then solve explicitly for the Fourier coefficients $\mathcal{M}_{n,l}$.

In the general asymmetric case, we find that

$$\mathcal{M}_{n,l} = \frac{1}{Lk_l}(-1)^{l+1}\left[2F_n^* + \left(\frac{F_{1-n}^*}{\widetilde{W}_{1-n}(0)} - \frac{F_n^*}{\widetilde{W}_n(0)}\right)b_l\right], \tag{2.52}$$

on setting

$$\begin{aligned} b_l &= \frac{2\widetilde{W}_{1-n}(Dk_l^2)\widetilde{W}_n(Dk_l^2)}{\widetilde{W}_{1-n}(Dk_l^2) + \widetilde{W}_n(Dk_l^2)\widetilde{\omega}_{1-n}(Dk_l^2)} \\ &= \frac{2}{\left(\widetilde{W}_n(Dk_l^2)\right)^{-1} + \left(\widetilde{W}_{1-n}(Dk_l^2)\right)^{-1} - Dk_l^2}, \end{aligned} \tag{2.53}$$

and using the relation $\widetilde{\omega}_n(Dk_l^2) = 1 - Dk_l^2\widetilde{W}_n(Dk_l^2)$. Note that b_l is independent of the value of n and that the steady-state solution is again independent of the initial data as expected.

Using the sine transform of the linear function $y = x/L$, (2.52) can be rewritten as

$$M_0(x) = \frac{x}{L}F_0^* - \left(\frac{F_0^*}{\widetilde{W}_0(0)} - \frac{F_1^*}{\widetilde{W}_1(0)}\right)\sum_{l=1}^{\infty} a_l \sin(k_l x), \tag{2.54a}$$

$$M_1(x) = \frac{x}{L}F_1^* + \left(\frac{F_0^*}{\widetilde{W}_0(0)} - \frac{F_1^*}{\widetilde{W}_1(0)}\right)\sum_{l=1}^{\infty} a_l \sin(k_l x), \tag{2.54b}$$

where for compactness we have set

$$a_l = \frac{(-1)^{l+1}}{Lk_l}b_l. \tag{2.55}$$

Note that $\widetilde{W}_n(0)$ is the mean time to leave state n, denoted by $\mathbb{E}[T_n]$, and that adding $M_1(x)$ and $M_0(x)$ recovers the linear function $M(x)$.

Enforcing the Neumann boundary condition and solving for F_n^* in terms of the other boundary value F_{1-n}^*, we arrive at

$$F_n^* = F_{1-n}^* \frac{\widetilde{W}_n(0)\sum_{l=1}^{\infty} b_l}{\widetilde{W}_n(0)\widetilde{W}_{1-n}(0) + \widetilde{W}_{1-n}(0)\sum_{l=1}^{\infty} b_l}, \quad k_l = \frac{\pi l}{L}. \tag{2.56}$$

Now recall from (2.15) that $M(x) = K_0 x$ on $x \in [0, L)$. Hence, adding (2.54) implies that

$$K_0 = \frac{F_0^* + F_1^*}{L} \tag{2.57}$$

and setting $n = 1$, we calculate

$$F_1^* = K_0 L \frac{\widetilde{W}_1(0) \sum_{l=1}^\infty b_l}{\widetilde{W}_0(0)\widetilde{W}_1(0) + \big(\widetilde{W}_0(0) + \widetilde{W}_1(0)\big) \sum_{l=1}^\infty b_l}. \tag{2.58}$$

In the symmetric case $\alpha_0(\tau) = \alpha_1(\tau) \equiv \alpha(\tau)$, set $W_n = W$, etc. The above results reduce to

$$b_l = \frac{2\widetilde{W}(Dk_l^2)}{1 + \widetilde{\omega}(Dk_l^2)} = \frac{2(1 - \widetilde{\omega}(Dk_l^2))}{Dk_l^2(1 + \widetilde{\omega}(Dk_l^2))} \tag{2.59}$$

with the simpler expression for the unknown boundary value

$$F_1^* = K_0 L \frac{\sum_{l=1}^\infty b_l}{\widetilde{W}(0) + 2\sum_{l=1}^\infty b_l}, \tag{2.60}$$

where $\widetilde{W}(0)$ is the mean time between switching events.

We can now use this result to calculate the effective permeability of an interior gate separating two cellular domains.

2.4. Calculation of permeability. Our main goal is to calculate the effective permeability, which depends on the steady-state flux $J_0 = -DK_0$. In order to determine K_0, we have to repeat the above analysis for the corresponding boundary value problem on $x \in (L, 2L)$:

$$\frac{\partial M_n(x,t)}{\partial t} = D\frac{\partial^2 M_n(x,t)}{\partial x^2} - N_n(x,t) + N_{1-n}(x,t), \quad x \in (L, 2L), \tag{2.61}$$

with boundary conditions

$$M_0(L,t) = G_0(t), \quad \partial_x M_1(L,t) = 0, \quad M_n(2L,t) = \eta\lambda_n(t). \tag{2.62a}$$

Also, define the boundary value of $M_1(x,t)$ at the right side of the gate by $M_1(L^+,t) = G_1(t)$. It is convenient to perform the change of variables $y = 2L - x$ with $y \in [0, L)$ and to set $Q_n(y,t) = M_n(2L - y, t) - \lambda_n(t)\eta$. The second condition ensures that Q_0 and Q_1 vanish at $x = 0$, so that they can be extended to odd periodic functions on $[-L, L]$ as before. Note that these transformations do not change the governing PDE, and the boundary conditions on the new domain are

$$Q_n(0,t) = 0, \quad Q_0(L,t) = G_0(t) - \eta\lambda_0(t), \quad \partial_y Q_1(L,t) = 0. \tag{2.63}$$

We can thus immediately write down the steady-state solution for $W_n(y)$ (see (2.54)):

$$Q_0(y) = \frac{y}{L}\widehat{F}_0^* - \left(\frac{\widehat{F}_0^*}{\widetilde{W}_0(0)} - \frac{\widehat{F}_1^*}{\widetilde{W}_1(0)}\right)\sum_{l=1}^\infty a_l \sin(k_l y), \tag{2.64a}$$

$$Q_1(y) = \frac{y}{L}\widehat{F}_1^* + \left(\frac{\widehat{F}_0^*}{\widetilde{W}_0(0)} - \frac{\widehat{F}_1^*}{\widetilde{W}_1(0)}\right)\sum_{l=1}^\infty a_l \sin(k_l y) \tag{2.64b}$$

with $\widehat{F}_n^* = G_n^* - \eta\lambda_n^*$ and $G_n^* = \lim_{t\to\infty} G_n(t)$. Moreover,

$$\widehat{F}_n^* = \widehat{F}_{1-n}^* \frac{\widetilde{W}_n(0)\sum_{l=1}^\infty b_l}{\widetilde{W}_n(0)\widetilde{W}_{1-n}(0) + ilW_{1-n}(0)\sum_{l=1}^\infty b_l}. \tag{2.65}$$

Now recall from (2.15) that $M(x) = K_0(x - 2L) + \eta$ on $x \in (L, 2L]$, which implies $Q(y) = Q_0(y) + Q_1(y) = -K_0 y$. Hence, adding (2.64) shows that

$$K_0 = -\frac{\widehat{F}_0^* + \widehat{F}_1^*}{L} = \frac{\eta - G_0^* - G_1^*}{L}. \tag{2.66}$$

and

$$G_1^* - \lambda_1^* \eta = -K_0 L \frac{\widetilde{W}_1(0)\sum_{l=1}^\infty b_l}{\widetilde{W}_0(0)\widetilde{W}_1(0) + \big(\widetilde{W}_0(0) + \widetilde{W}_1(0)\big)\sum_{l=1}^\infty b_l}. \tag{2.67}$$

To calculate the slope K_0, all that is left is to enforce the matching condition $M_0(L^-) = M_0(L^+)$. Using $M_0(x) = M(x) - M_1(x)$, this condition becomes

$$M(L^-) - M_1(L^-) = M(L^+) - M_1(L^+)$$

or

$$K_0 L - F_1^* = -K_0 L + \eta - G_1^*. \tag{2.68}$$

Substituting for F_1^* and G_1^*, we arrive at

$$\begin{aligned} K_0 L - K_0 L &\frac{\widetilde{W}_1(0)\sum_{l=1}^\infty b_l}{\widetilde{W}_0(0)\widetilde{W}_1(0) + \big(\widetilde{W}_0(0) + \widetilde{W}_1(0)\big)\sum_{l=1}^\infty b_l} \\ &= -K_0 L + \eta - \lambda_1^*\eta + K_0 L \frac{\widetilde{W}_1(0)\sum_{l=1}^\infty b_l}{\widetilde{W}_0(0)\widetilde{W}_1(0) + \big(\widetilde{W}_0(0) + \widetilde{W}_1(0)\big)\sum_{l=1}^\infty b_l}, \end{aligned}$$

which can be rearranged to determine K_0 and hence J_0:

$$J_0 = -\frac{D\eta\lambda_0^*}{2L}\left(1 - \frac{\widetilde{W}_1(0)\sum_{l=1}^\infty b_l}{\widetilde{W}_0(0)\widetilde{W}_1(0) + \big(\widetilde{W}_0(0) + \widetilde{W}_1(0)\big)\sum_{l=1}^\infty b_l}\right)^{-1}. \tag{2.69}$$

Finally, comparing with (1.5), we obtain the effective permeability

$$\frac{1}{\mu_e} = \frac{2L\lambda_1^*}{D\lambda_0^*}\frac{\widetilde{W}_0(0)\widetilde{W}_1(0) + \big(\widetilde{W}_0(0) - \frac{\lambda_0^*}{\lambda_1^*}\widetilde{W}_1(0)\big)\sum_{l=1}^\infty b_j}{\widetilde{W}_0(0)\widetilde{W}_1(0) + \big(\widetilde{W}_0(0) + \widetilde{W}_1(0)\big)\sum_{l=1}^\infty b_j}. \tag{2.70}$$

This can be simplified by noting that we can rewrite (2.28a) as

$$\lambda_n^* = \frac{\mathbb{E}[T_n]}{\mathbb{E}[T_{1-n}] + \mathbb{E}[T_n]} = \frac{\widetilde{W}_n(0)}{\widetilde{W}_n(0) + \widetilde{W}_{1-n}(0)}, \tag{2.71}$$

reducing the effective permeability to

$$\frac{1}{\mu_e} = \frac{2L\widetilde{W}_1(0)}{D\widetilde{W}_0(0)}\frac{1}{1 + \left(\left(\widetilde{W}_0(0)\right)^{-1} + \left(\widetilde{W}_1(0)\right)^{-1}\right)\sum_{l=1}^\infty b_l}. \tag{2.72}$$

This quantity depends on the length of the domain and the statistics of the gate through the Fourier modes k_l by way of the $\widetilde{W}_n(Dk_l^2)$ terms present in b_l. For symmetric switching rates this permeability can be reduced to

$$\frac{1}{\mu_e} = \frac{2L}{D}\frac{\widetilde{W}(0)}{\widetilde{W}(0) + 2\sum_{l=1}^\infty b_j}, \tag{2.73}$$

which reduces to the previous permeability in the case of symmetric switching rates.

Note that (2.54) and (2.64) automatically satisfy the flux continuity condition $\partial_x M_0(L_-) = \partial_x M_0(L_+)$, since

$$\partial_x M_0(L_-) = \frac{F_0^* + F_1^*}{L} = K_0$$

and

$$\partial_x M_0(L_+) = -\partial_y Q_0(L_-) = -\frac{\widehat{F}_0^* + \widehat{F}_1^*}{L} = K_0$$

is an immediate condition of imposing the solution (2.15) for $M(x)$.

Since the effective permeability μ_e can theoretically take on values anywhere in the range $(0, \infty)$, it is not always the easiest characteristic of the system to gain information from. Other options are the gradient K_0 and the jump in density across the gate U. These three characteristics, μ_e, K_0, and U, of the steady-state solution are related to each other by $U = \eta - 2LK_0$ and $\mu_e = \frac{-J_0}{U} = D\frac{K_0}{U}$. We will use U in plotting since it gives better graphical information than the effective permeability or the steady-state gradient, taking on values in $(0, \eta)$. Finally, it is worth noting that for symmetric switching, the effective permeability is restricted to $(\frac{D}{2L}, \infty)$, and the jump discontinuity is likewise restricted to $[0, 1/2)$. In order to restrict movement across the gate further, asymmetric switching rates are needed.

3. Particle perspective. In this section, we show that the solution to the stochastic PDE given by (1.1), (1.3), and (1.7) is a certain statistic of a single Brownian particle diffusing in a stochastically fluctuating environment. In addition to providing a simple probabilistic interpretation of the stochastic PDE, this representation enables efficient numerical approximation of the solution of the PDE by Monte Carlo simulations of a single diffusing particle.

Before deriving our results, we put them in the context of prior work. Representing solutions to deterministic PDEs in terms of statistics of Brownian motion has a long history, dating back over 70 years to Kakutani, Kac, and Doob [12, 22, 23]. Recently, we have shown that solutions to PDEs with stochastically switching boundary conditions can be represented by statistics of a Brownian particle in a stochastic environment [3] (see also [28, 6, 29, 30]). In [3], we assumed that the boundary condition switching times were exponentially distributed, which simplified the analysis in that (a) there was a simple transformation between the equations describing the forward time evolution of the mean PDE and the backward time evolution of statistics of the particle and (b) statistics of the switching boundary condition were independent of the direction of time.

However, these simplifications do not hold in the present work since the times between transitions of the gate are not exponentially distributed. In order to handle this more complicated situation, we employ techniques from stochastic analysis. Since these techniques are less common in the applied mathematics literature, we first introduce our basic approach with a simple example of the method of characteristics. Consider the deterministic PDE,

$$\frac{\partial}{\partial t}u(x,t) = b(x)\frac{\partial}{\partial x}u(x,t), \quad x \in \mathbb{R}, t > 0; \quad u(x,0) = \phi(x), \tag{3.1}$$

and suppose $\{X(s)\}_{s\geq 0}$ satisfies the deterministic ordinary differential equation and initial condition

$$\frac{\mathrm{d}X}{\mathrm{d}s} = b(X(s)), \quad s \in (0,T]; \quad X(0) = x \in \mathbb{R}. \tag{3.2}$$

(In order to match the subsequent stochastic analysis, we evolve X backward in time.)

Fix $T > 0$ and define the function

$$Z(s) := u(X(s), T - s), \quad s \in [0, T]. \tag{3.3}$$

Differentiating Z and using the chain rule and (3.1)–(3.2) implies that Z is constant,

$$Z'(s) = \frac{\partial}{\partial x} u(X(s), T - s) \frac{\mathrm{d}X}{\mathrm{d}s} - \frac{\partial}{\partial t} u(X(s), T - s) = 0. \tag{3.4}$$

Hence, $Z(0) = Z(T)$, which upon using (3.1)–(3.2) implies that

$$u(x, T) = \phi(X(T)). \tag{3.5}$$

In other words, (3.5) states that the solution to the PDE (3.1) can be represented as a function or "statistic" of the "particle" X. Below, we extend this argument to solve the stochastic PDE given by (1.1), (1.3), and (1.7) using tools from stochastic analysis, including Itô's formula, local times, and stopping times [24].

3.1. Probabilistic representation. Consider a single particle diffusing in the interval $[0, 2L]$ with diffusivity $D > 0$ and reflecting boundary conditions at the endpoints $x = 0$ and $x = 2L$. Suppose the particle diffuses in the presence of a stochastic gate $\{\overline{n}(s)\}_{s \geq 0}$ at $x = L$, so that the particle is reflected at $x = L$ when the gate is closed ($\overline{n} = 1$) and diffuses freely past $x = L$ when the gate is open ($\overline{n} = 0$). In order to relate statistics of this single particle to the solution of the stochastic PDE given by (1.1), (1.3), and (1.7), we need to suppose that the gate experienced by the particle, $\{\overline{n}(s)\}_{s \geq 0}$, is the time reversal of the gate experienced by the PDE, $\{n(t)\}_{t \geq 0}$.

Specifically, fix a positive time $T > 0$ and let $X(s) \in \mathbb{R}$ denote the position of a diffusing particle at time $s \in [0, T]$ which satisfies the stochastic differential equation (SDE),

$$\mathrm{d}X(s) = \sqrt{2D}\, \mathrm{d}W(s) + \overline{n}(s) S_T(s)\, \mathrm{d}K_L(s) + \mathrm{d}K_0(s) - \mathrm{d}K_{2L}(s), \tag{3.6}$$

where $\overline{n}$ is the time reversal of n,

$$\overline{n}(s) := n(T - s), \quad s \in [0, T], \tag{3.7}$$

and $\{W(s)\}_{s \geq 0}$ is a standard Brownian motion that is independent of $\{n(t)\}_{t \geq 0}$. Furthermore,

$$S_T(s) := \begin{cases} -1 & \text{if } X\big(s - R(T - s)\big) \leq L, \\ 1 & \text{if } X\big(s - R(T - s)\big) > L, \end{cases} \tag{3.8}$$

where $R(t)$ is the time until $n(t)$ switches (often called the residual in renewal theory),

$$R(t) := \sup\{h > 0 : n(t + \sigma) = n(t) \text{ for all } \sigma \in [0, h]\},$$

and $K_x(s)$ is the local time [24] of $X(s)$ at $x \in \{0, L, 2L\}$. That is, $K_x(s)$ is nondecreasing and increases only when $X(s) = x$. Formally, the local time that a diffusing particle spends at a location x is defined by

$$K_x(s) = \lim_{\varepsilon \to 0^+} \frac{1}{2\varepsilon} \int_0^s 1_{\{x - \varepsilon, x + \varepsilon\}} ds, \tag{3.9}$$

where $1_{\{x-\varepsilon, x+\varepsilon\}}$ is the indicator function for the interval $(x - \varepsilon, x + \varepsilon)$. The significance of the second local time term $\mathrm{d}K_0(s)$ in (3.6) is that it forces $X(s)$ to reflect from

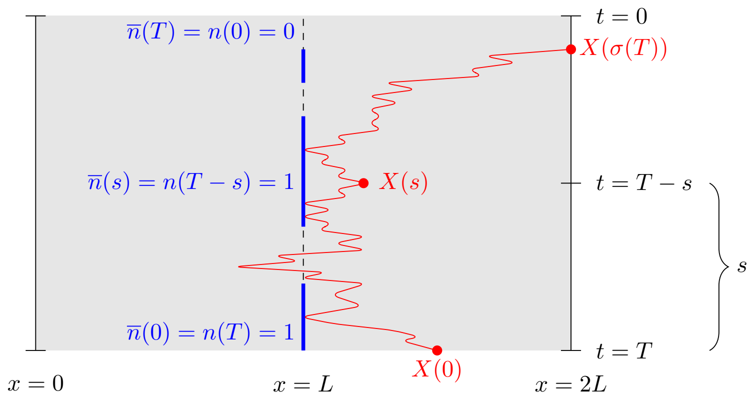

FIG. 3.1. *Single particle diffusing in the presence of a stochastic gate. The gate experienced by the particle is the time reversal of the gate experienced by the PDE.*

$x = 0$, and the final local time term $\mathrm{d}K_{2L}(s)$ in (3.6) forces $X(s)$ to reflect from $x = 2L$. Similarly, the first local time term in (3.6) forces $X(s)$ to reflect from $x = L$ when $n(T-s) = 1$. The direction of reflection is determined by whether the particle was to the left or the right of $x = L$ when the gate closed, which is described by (3.8). Intuitively, we can think of $\mathrm{d}K_{x_0}(s)$ as an instantaneous positive unit impulse $\delta(X(s) - x_0)ds$ whenever a diffusing particle hits $x = x_0$. Summed together, the local time terms incorporate the reflecting boundary conditions and the geometry of the domain into the SDE (3.6) for the diffusing particle. Figure 3.1 summarizes this setup.

Below, we use $\mathbb{E}_x$ to denote expectation conditioned on the initial particle position,

$$X(0) = x \in [0, 2L]. \tag{3.10}$$

We also use $\mathbb{E}_x[\,\cdot\,|\,n]$ to denote expectation conditioned on (3.10) and a realization of the gate, $n = \{n(t)\}_{t\geq 0}$. Analogously, $\mathbb{P}_x$ and $\mathbb{P}_x(\,\cdot\,|\,n)$ denote the associated probability measures.

To find a relationship between the solution $u(x,t)$ to (1.1), (1.3), and (1.7) and statistics of X, we define the stochastic process (which is analogous to (3.3) above),

$$Z(s) := u(X(s), T-s), \quad s \in [0,T].$$

Note that Z is formed from evaluating the stochastic function u at a spatial coordinate determined by the stochastic position of the particle X. Hence, Z depends on the gate $\{n(t)\}_{t\in[0,T]}$ and the path of the particle $\{X(s)\}_{s\in[0,T]}$. As in (3.4) above, we now want to differentiate Z. However, since Z is stochastic, we use the stochastic version of the chain rule known as Itô's formula [24] to obtain

$$\begin{aligned} Z(s) - Z(0) &= u(X(s), T-s) - u(X(0), T) \\ &= \int_0^s \Big(-\frac{\partial}{\partial t} + D\frac{\partial^2}{\partial x^2}\Big)u(X(s'), T-s')\,\mathrm{d}s' \\ &\quad + \int_0^s n(T-s')S_T(s')\frac{\partial}{\partial x}u(X(s'), T-s')\,\mathrm{d}K_L(s') \\ &\quad + \int_0^s \frac{\partial}{\partial x}u(X(s'), T-s')\,\mathrm{d}K_0(s') - \int_0^s \frac{\partial}{\partial x}u(X(s'), T-s')\,\mathrm{d}K_{2L}(s') + M, \end{aligned} \tag{3.11}$$

where M satisfies $\mathbb{E}_x[M|n] = 0$. As a technical aside, Itô's formula holds for twice differentiable functions, but u is (i) discontinuous in time at $x = L$ when the gate opens or closes and (ii) discontinuous in space at $x = L$ while the gate is closed. However, we can ignore technicality (i) because the particle is almost surely not at $x = L$ when the gate opens or closes. This can be made rigorous by introducing the left derivative with respect to the time variable s

$$\frac{\partial^-}{\partial s} f(s) = \lim_{\varepsilon \to 0^+} \frac{f(s) - f(s-\varepsilon)}{\varepsilon} \tag{3.12}$$

and using a generalized Itô's formula for functions continuous almost everywhere in time [16]. Noting that the set of times of the switching events T_n have measure zero and that

$$\frac{\partial^-}{\partial s} u(x, T-s) = -\frac{\partial^+}{\partial t} u(x, T-s), \tag{3.13}$$

where $\frac{\partial^+}{\partial t}$ is the analogously defined right derivative, the generalized Itô's formula then states that (3.11) with $\frac{\partial}{\partial t}$ replaced by $\frac{\partial^+}{\partial t}$ holds almost surely. This leads to the same result as our formulation. Point (ii) is taken care of through the term involving $\mathrm{d}K_L(s)$, as the particle reflects at $x = L$ while the gate is closed due to the addition of a boundary after the domain changes form (and thus cannot cross $x = L$, so the discontinuity is irrelevant).

Now, define the stopping time

$$\sigma(T) := \inf\big\{s \in [0, T] : X(s) \in \{0, 2L\}\big\}, \tag{3.14}$$

which is the first time the particle reaches $x = 0$ or $x = 2L$ (or $\sigma(T) = \infty$ if the particle does not reach one of these points before time T). Next, if we evaluate (3.11) at s equal to the minimum of $\sigma(T)$ and T and use the PDE in (1.1), the definition of $\sigma(T)$ in (3.14), and the boundary conditions in (1.7), then we find that

$$u\Big(X\big(\min\{\sigma(T), T\}\big), T - \min\{\sigma(T), T\}\Big) - u(X(0), T) = M. \tag{3.15}$$

Since $\mathbb{E}_x[M|n] = 0$, taking the expected value of (3.15) conditioned on a realization $n = \{n(t)\}_{t\geq 0}$ of the gate implies

$$\begin{aligned} \mathbb{E}_x[u(X(0), T) \,|\, n] = \mathbb{E}_x[&u\big(X(\sigma(T)), T - \sigma(T)\big) 1_{\sigma(T)\leq T} 1_{X(\sigma(T))=0} \,|\, n] \\ &+ \mathbb{E}_x[u\big(X(\sigma(T)), T - \sigma(T)\big) 1_{\sigma(T)\leq T} 1_{X(\sigma(T))=2L} \,|\, n] \\ &+ \mathbb{E}_x[u\big(X(T), 0\big) 1_{\sigma(T)>T} \,|\, n]. \end{aligned} \tag{3.16}$$

Since $u(x, T)$ is measurable with respect to $\{n(t)\}_{t\geq 0}$, we have that

$$\mathbb{E}_x[u(X(0), T) \,|\, n] = u(x, T). \tag{3.17}$$

Furthermore, the definition of $\sigma(T)$ in (3.14) and the boundary conditions in (1.3) imply

$$u\big(X(\sigma(T)), T - \sigma(T)\big) 1_{\sigma(T)\leq T} 1_{X(\sigma(T))=0} = 0, \tag{3.18}$$

$$u\big(X(\sigma(T)), T - \sigma(T)\big) 1_{\sigma(T)\leq T} 1_{X(\sigma(T))=2L} = \eta. \tag{3.19}$$

Therefore, assuming the simple initial condition

$$u(x,0)=0,\quad x\in(0,L), \tag{3.20}$$

(3.16)–(3.19) imply

$$u(x,T)=\eta\mathbb{P}_x(\sigma(T)\le T\cap X(\sigma(T))=2L\,|\,n). \tag{3.21}$$

We note that our analysis does not require the initial condition (3.20), but the relation in (3.21) simplifies under this assumption.

To understand (3.21), note that the two independent sources of randomness in the system are (i) the realization of the stochastic gate $\{n(t)\}_{t\ge0}$ and (ii) the Brownian motion $\{W(s)\}_{s\ge0}$ driving the path of the particle $\{X(t)\}_{s\ge0}$. Equation (3.21) is an average over the Brownian motion for a fixed realization of the gate. That is, (3.21) depends on the stochastic realization of gate, but the randomness from the Brownian motion has been averaged out.

If we then average (3.21) over realizations of the gate, then we find that

$$\mathbb{E}[u(x,T)]=\eta\mathbb{P}_x(\sigma(T)\le T\cap X(\sigma(T))=2L). \tag{3.22}$$

Since we are interested in the large time behavior of the mean of u, we take $T\to\infty$ in (3.22) to obtain

$$\lim_{T\to\infty}\mathbb{E}[u(x,T)]=\eta\lim_{T\to\infty}\mathbb{P}_x(X(\sigma(T))=2L), \tag{3.23}$$

where we have used that $\mathbb{P}_x(\sigma(T)\ge T)\to0$ as $T\to\infty$.

To summarize, (3.23) states that the large time mean of the solution to the stochastic PDE given by (1.1), (1.3), and (1.7), evaluated at a point $x\in[0,2L]$, is the inhomogeneous boundary condition η multiplied by the probability that a single particle starting at $x\in[0,2L]$ will reach $2L$ before 0, assuming the particle diffuses in the presence of a stochastic gate at $x=L$. This is commonly referred to as the splitting probability. Importantly, the statistics of the gate experienced by this single particle (denoted by $\{\overline{n}(s)\}_{s\ge0}$) are the same as the statistics of the gate experienced by the PDE (denoted by $\{n(t)\}_{t\ge0}$), except for two important differences. First, the gate experienced by this single particle is initially in state 0 with probability

$$\mathbb{P}(\overline{n}(0)=0)=\lambda_0^*=\widetilde{W}_0(0)/\big(\widetilde{W}_0(0)+\widetilde{W}_1(0)\big), \tag{3.24}$$

where $\widetilde{W}_n$ is the Laplace transform of the survival probability W_n defined in (2.19). That is, $W_n(t)$ is the probability that the gate $\{n(t)\}_{t\ge0}$ (the gate experienced by the PDE) has not switched after residing in state n for time $t\ge0$, and $\widetilde{W}_n(0)$ is the mean time spent in state n before switching. Equation (3.24) follows immediately from noting that (3.6)–(3.7) implies that the initial state of the gate experienced by the particle is $n(T)$ and $\lim_{T\to\infty}\mathbb{P}(n(T)=0)=\lambda_0^*$.

Second, the duration $\overline{\tau}>0$ that $\{\overline{n}(s)\}_{s\ge0}$ spends in its initial state (either open or closed) has the following distribution:

$$\mathbb{P}(\overline{\tau}\le t)=\lim_{T\to\infty}\mathbb{P}(\tau(T)\le t).$$

Again, this follows immediately from (3.6)–(3.7) and the definition of $\tau(T)$. The large

T distribution of $\tau(T)$ was shown in Lemma 2.6 of [27] to be

$$\lim_{T\to\infty} \mathbb{P}(\tau(T) \le t) = \mathbb{P}(\xi a^1 + (1-\xi)a^0 \le t), \tag{3.25}$$

where $\xi \in \{0,1\}$ is a Bernoulli random variable with $\mathbb{P}(\xi = 0) = \lambda_0^*$ and the distribution of a^n is

$$\mathbb{P}(a^n \le t) = \frac{1}{\widetilde{W}_n(0)} \int_0^t W_n(s)\,\mathrm{d}s. \tag{3.26}$$

We emphasize that this subtlety in the time spent in the initial state did not appear in our previous work, which assumed exponential switching times [3] because a^n is exponential under this assumption.

3.2. Approximating mean PDE solution by particle simulation. The theory developed in the previous subsection yields an algorithm for approximating $\lim_{t\to\infty} \mathbb{E}[u(x,t)]$ using an average of realizations of a single particle moving in the switching environment in place of an average of realizations of the full stochastic PDE. There is a bit of a tradeoff in terms of the numerical cost here. It often takes on the order of 10^5 trials per particle starting location to obtain accurate results; however, since the steady-state solution is piecewise linear, only a few starting locations near the gate and the ends of the domain are needed, and for reasonably small L the particle will exit the domain before the mean of the realizations of the PDE approaches steady state. It is also less costly to simulate Brownian motion than it is to numerically solve a PDE in general, especially considering that Monte Carlo trials are independent, and thus easily parallelizable.

It is key that when simulating single particles the initial length of time the gate is in its initial state $\overline{\tau}$ is chosen according to the age distribution given in (3.25), which assumes that the gate has been open for some previous amount of time already. To see both the improved accuracy of this method and how a naive particle simulation fails, we will consider symmetric switching with $\omega_0(\tau) = \omega_1(\tau) \equiv \omega(\tau) = 1_{[1,2]}$, a uniform distribution on $[1,2]$. With symmetric switching, the right-hand side of (3.25), the initial age distribution of the gate, simplifies to (3.26) with $W_0(\tau) = W_1(\tau) \equiv W(\tau)$. We generate an age a for the initial state of the gate using inverse transform sampling. In the case of a uniform distribution on $[\tau_1,\tau_2]$, this corresponds to

$$a(\rho) = \begin{cases} \frac{\tau_1+\tau_2}{2}\rho & \text{if } \rho \le \frac{2\tau_1}{\tau_1+\tau_2}, \\ \tau_2 - \sqrt{\tau_2^2-\tau_1^2}\sqrt{1-\rho}, & \text{if } \rho > \frac{2\tau_1}{\tau_1+\tau_2}, \end{cases}$$

where ρ is a uniform $[0,1]$ distributed random variable. We also perform a naive simulation where the duration of the initial state of the gate is simply chosen according to $\mathbb{P}(\overline{\tau} \le t) = W(t)$. The results of both simulations compared to the theoretical result predicted by the steady-state solution are shown in Figure 3.2. While the naive splitting probability estimate has the correct features, it is linear and has a jump in density at the gate, it also deviates from the true steady-state solution as the initial location of the particle approaches the gate. Near the gate the probability of the particle passing through or reflecting off the gate is much higher, so detailed initial statistics given by the age distribution $\mathbb{P}(a \le t)$ are needed to give a correct match.

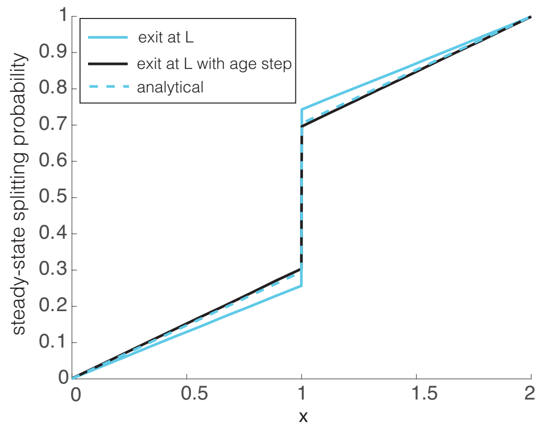

FIG. 3.2. *Analytical steady-state solution for the splitting probability (dashed light curve) compared against a naive simulation (solid blue curve) and a simulation with corrected statistics for* $\overline{\tau}$ *(black curve). Both* η *and* L *are set to* 1.

4. Examples of rate functions.

4.1. Markovian transition rates. We first consider the Markovian case of τ-independent rates $\alpha_n(\tau) = \alpha_n$, which was previously analyzed in [5]. It is a straightforward calculation to show that

$$\widetilde{W}_n(s) = \frac{1}{s + \alpha_n}.$$

The coefficient b_l in (2.53) reduces to

$$b_j = \frac{2}{\left(\widetilde{W}_n(Dk_l^2)\right)^{-1} + \left(\widetilde{W}_{1-n}(Dk_l^2)\right)^{-1} - Dk_l^2} = \frac{2}{\alpha_0 + \alpha_1 + Dk_l^2}, \tag{4.1}$$

and hence the effective permeability is

$$\frac{1}{\mu_e} = \frac{2L}{D}\frac{\alpha_0}{\alpha_1}\left[\sum_{l=1}^{\infty}\frac{2(\alpha_0 + \alpha_1)}{\alpha_0 + \alpha_1 + Dk_l^2} + 1\right]^{-1}. \tag{4.2}$$

Using the identity,

$$\sum_{l=1}^{\infty}\frac{2}{\alpha_0 + \alpha_1 + Dk_l^2} = \frac{\xi L \coth(\xi L) - 1}{\alpha_0 + \alpha_1}, \quad \text{where } \xi := \sqrt{(\alpha_0 + \alpha_1)/D},$$

it follows that (4.2) is equivalent to the result (1.8) from [5].

4.2. Age-structured transition rates. Consider a case where the transition from the closed state $n = 1$ to the open state $n = 0$ has a constant associated rate $\alpha_1(\tau) = \alpha$, while the transition from the open state to the closed state passes through $m - 1$ irreversible substates, $m \geq 1$, each with a constant associated rate α as well for simplicity. We assume the gate is still open while in these substates.

To model this using our age-structured formulation, we can construct a transition rate function $\alpha_0(\tau)$ such that the first passage time distribution from $n = 0$ directly

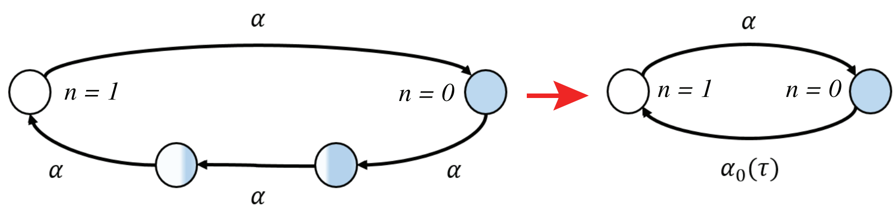

Fig. 4.1. *Reduction of a simple continuous time Markov process for the gate into an effective two-state age-structured process by using a phase-type distribution to collapse the intermediate states going from $n = 0$ to $n = 1$.*

to $n = 1$ using $\alpha_0(\tau)$ is the same as the distribution associated with passing through $m - 1$ substates with constant rates. This is equivalent to constructing a phase-type distribution from state $n = 0$ to state $n = 1$ since we started with a continuous-time Markov process (see Figure 4.1). Since the transition from open to closed is independent and identically distributed exponentially for each transition between substates, the first passage time from open to closed has a gamma distribution with shape parameter m and rate parameter α. Therefore we have

$$\omega_1(\tau) = \alpha e^{-\alpha\tau}, \quad \omega_0(\tau) = \frac{\alpha^m}{(m-1)!}\tau^{m-1}e^{-\alpha\tau}. \tag{4.3}$$

The associated Laplace transforms for ω_n and W_n are

$$\widetilde{\omega}_1(s) = \alpha(s+\alpha)^{-1}, \quad \widetilde{\omega}_0(s) = \alpha^m(s+\alpha)^{-m}, \tag{4.4}$$

$$\widetilde{W}_1(s) = \frac{1}{s+\alpha}, \quad \widetilde{\omega}_0(s) = \frac{1-\alpha^m(s+\alpha)^{-m}}{s}, \tag{4.5}$$

with $\widetilde{W}_1(0) = 1/\alpha$, $\widetilde{W}_0(0) = m/\alpha$. Substituting this into (2.72), the resulting effective permeability can be written as

$$\frac{1}{\mu_e} = \frac{2L}{D}\frac{1}{m + \alpha(m+1)\sum_{l=1}^{\infty} b_l}, \tag{4.6}$$

where the coefficients b_l take the form

$$b_l = \frac{2\left((Dk_l^2+\alpha)^m - \alpha^m\right)}{(Dk_l^2+\alpha)^{m+1} - \alpha^{m+1}} \sim \frac{2}{Dk_l^2 + (m+1)\alpha} \text{ for large } l, \tag{4.7}$$

and the jump in density U at the gate is

$$U = \eta\frac{m}{1+m}\frac{m}{m + \alpha\sum_{l=1}^{\infty} b_l}. \tag{4.8}$$

This result matches one's intuition, namely, if the number of substates increases, the time needed on average for the gate to close will increase, increasing the effective permeability, and thus decreasing the jump at the gate (see Figure 4.2(a)). In the case $m = 1$ when there are no intermediate states, the permeability reduces to what was found in the Markovian case in the previous section if one imposes symmetric switching rates $\alpha_0 = \alpha_1$.

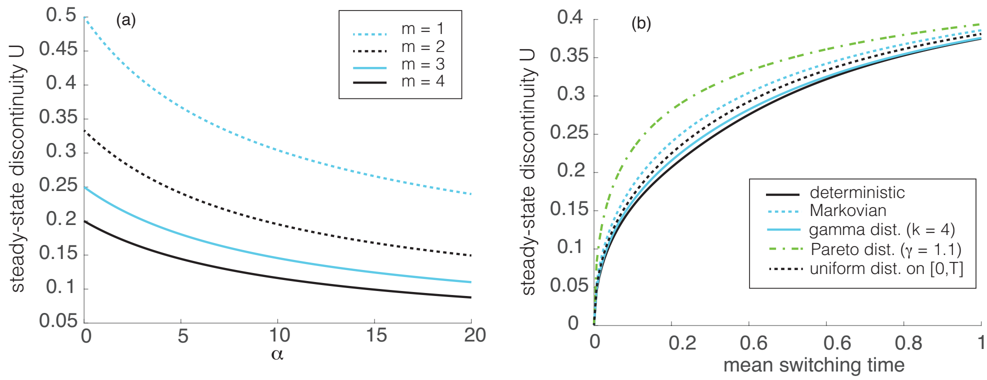

FIG. 4.2. *Steady-state jump discontinuity U of the concentration at the gap junction with a switching gate.* (a) *Plot of U against switching rate α for the age-structured switching distribution given in* (4.3). (b) *Plot of U against mean switching time for the various distributions given in* (4.9). *We set $\eta = L = 1$ in all plots.*

4.3. Jump discontinuity U as a function of mean switching time. When comparing the effects of different switching time distributions, it is helpful to compare them by fixing the mean switching time, then comparing the jump discontinuity U at the gate for each distribution. We will consider five distributions with symmetric switching: deterministic, exponential (Markovian), gamma, Pareto, and uniform, given, respectively, by

$$\begin{aligned}
&\omega_d(\tau) = \delta(\tau - t_0),\\
&\omega_e(\tau) = \alpha e^{-\alpha\tau},\\
&\omega_g(\tau) = \frac{1}{\Gamma(k)\beta^k}\tau^{k-1}e^{-\frac{\tau}{\beta}} \quad \text{with } k = 4,\\
&\omega_p(\tau) = \begin{cases} 0 & \text{if } \tau < \tau_0,\\ \frac{\gamma\tau_0^\gamma}{\tau^{\gamma+1}} & \text{if } \tau \geq \tau_0 \end{cases} \quad \text{with } \gamma = 1.1,\\
&\omega_u(\tau) = \frac{1}{\tau_1}1_{[0,\tau_1]}
\end{aligned} \tag{4.9}$$

with means given, respectively, by t_0, $1/\alpha$, βk, $\gamma\tau_0/(\gamma-1)$, and $\tau_1/2$. In the case of deterministic switching ($\omega_d(\tau) = \delta(t - t_0)$), we assume the initial switching time is uniformly distributed on $[0, t_0]$ so that the large time limit of the mean solution exists.

If we fix a mean switching time $\mathbb{E}[T]$, then we obtain the following results for the jump discontinuity at the gate (see also Figure 4.2(b)). First, all the jump discontinuities have the same overall behavior, starting at 0 in the case of fast switching, and saturating at 0.5 (since we have symmetric switching with $\eta = 1 = L$) in the slow switching limit. However, there is a clear ordering based on the various distributions, which is related to the second moment $\mathbb{E}[T^2]$ of the switching time. Perhaps unsurprisingly, a larger second moment or variance results is a greater value of U, since it allows greater times between conformational changes to the gate. We will use subscripts to distinguish between expected values for various distributions. Formulating $\mathbb{E}[T^2]$ in terms of $\mathbb{E}[T]$ where possible, we have $\mathbb{E}_p[T^2] = \infty$ for the Pareto distribution since $\gamma < 2$, $\mathbb{E}_e[T^2] = (\mathbb{E}_e[T])^2$ for the exponential distribution, $\mathbb{E}_u[T^2] = (\mathbb{E}_u[T])^2/3$

for the uniform distribution, $\mathbb{E}_g[T^2] = (\mathbb{E}_g[T])^2/4$ for the gamma distribution since $k = 4$, and $\mathbb{E}_d[T^2] = 0$ for the deterministic delta distribution.

5. Discussion. In this paper, we extended recent work on determining the effective permeability of a stochastically gated gap junction to the case of age-structured switching [5]. Using the method of characteristics and Fourier/Laplace transforms, we solved the PDEs for the first moments of the stochastic concentration, conditioned on the state of the gate and after integrating out the residence time τ of the age-structured process. This allowed us to determine the mean jump discontinuity of the concentration at the gap junction and thus the effective permeability, which depends on the diffusive speed D as well as the length of the domain L. We conjecture that this dependence on the distance from the particle source to the gate also holds in more complex geometries and that the dependence on this distance vanishes in the limit or a far-field source.

Using a corresponding single particle representation of the stochastic process that takes into account the changing environment, we showed that the results of our analysis matched numerical results from Monte Carlo simulations. One challenging problem is how to generalize the analysis of a single age-structured gap junction to a one-dimensional array of N gap junctions. If the gap junctions independently switch, then one has to assign an age-structured discrete random variable $n_k(t,\tau) \in \{0,1\}$ to each gate, $k = 1,\ldots,N$. An upper bound on the permeability can be obtained by assuming that the gates switch simultaneously; however, this has complications as well. It is highly nontrivial to calculate how the memory of each gate propagates through space and interacts with the memory of other gates. Even in the memoryless case, the resulting system of equations is nontrivial to solve, which is why we have focused on the analysis of a single gate.

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