PAPER

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Diffusion in an age-structured randomly switching environment

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Abstract

Age-structured processes are well-established in population biology, where birth and death rates often depend on the age of the underlying populations. Recently, however, different examples of age-structured processes have been considered in the context of cell motility or certain types of stochastically gated ion channels, where the state of the system is determined by a switching process with age-dependent transition rates. In this paper we consider the particular problem of diffusion on a finite interval, with randomly switching boundary conditions due to the presence of an age-structured stochastic gate at one end of the interval. When the gate is closed the particles are reflected, whereas when it is open the domain is in contact with a particle bath. We use a moments method to derive a partial differential equation for the expectations of the stochastic concentration, conditioned on the state of the gate. We then use transform methods to eliminate the residence time of the age-structured switching, resulting in non-Markovian equations for the expectations, and determine the effective steady-state concentration gradient. Our analytical results are shown to match those obtained using Monte Carlo simulations.

Keywords: age-structured, diffusion, stochastic gating, random environment, characteristics

(Some figures may appear in colour only in the online journal)

1. Introduction

This paper is a continuation of a sequence of recent mathematical studies of diffusion processes in randomly switching environments [3–5, 18, 20]. The environment is taken to be a bounded domain with either randomly switching exterior boundary conditions or stochastically-gated internal barriers such as gap junctions. The stochastic switching is modeled by a

Markov chain whose transition rates are independent of the population density. The fact that the diffusing particles are all subject to the same fluctuating environment means that statistical correlations arise at the population level. That is, solving the diffusion equation for a particular realization of the stochastically switching boundary conditions yields a population density that depends on the particular realization. Hence, the density is a random field whose moments evolve according to a hierarchy of deterministic partial differential equations (PDEs) [3, 20]. This new type of model has applications to a variety of problem domains in biology and biophysics, including diffusion-limited reactions [6], insect physiology [8], stochastically-gated signaling between cells [7, 9], and volume neurotransmission [19, 21].

Probably the simplest example of the above type of process is the one-dimensional diffusion equation on a bounded interval [3, 18]. Suppose that the left-hand end satisfies a Dirichlet boundary condition, whereas the right-hand end switches between inhomogeneous Dirichlet and Neumann boundary conditions. The switching is represented by a two-state Markov chain. One finds that the solution of the stochastic diffusion equation converges in distribution to a random concentration whose expectation satisfies a deterministic system of partial differential equations PDEs. The solution of the latter is a linear function of x, with the underlying stochastic process reflected by the non-trivial dependence of the concentration gradient on model parameters.

In this paper we extend the one-dimensional problem to the case of age-structured switching. Age-structured processes are well known in population biology, where birth and death rates often depend on the age of the underlying population element [10, 15], which could be a cell undergoing differentiation or proliferation [23, 24, 26], or a whole organism undergoing reproduction [17]. Recently, however, a different example of an age-structured process has been considered within the context of cell motility [11–13]. The latter authors develop a stochastic two-state velocity jump model of cell motility, in which the switching rate depends upon the residence or running time the cell has spent moving in one direction. (This time is reset to zero each time a reversal of direction occurs.) If the switching rate is taken to be a decreasing function of the residence time, then one obtains a power law for the velocity switching time distribution. In particular, the cell undergoes a persistent random walk, whereby the longer the cell moves in a particular direction, the smaller the switching probability for reversing direction becomes. The resulting cell motility on mesoscopic time scales exhibits non-Markovian superdiffusive behavior consistent with some recent experimental studies [1, 16].

We adapt the analysis of Fedotov *et al* [11–13] in order to consider an age-structured switching process that controls the opening and closing of a stochastic gate at the right-hand end of a bounded interval containing a population of diffusing particles. When the gate is closed the particles are reflected, whereas when it is open the domain is in contact with a particle bath. After formulating the model in section 2, we extend the moments method of [3] to derive PDEs for the expectation of the stochastic concentration, conditioned on the age-structured state of the gate (section 3). We then use transform methods to eliminate the residence time, resulting in non-Markovian equations for the expectations, which are solved using Fourier/Laplace transforms and the method of characteristics (section 4). Finally, in section 5 we determine the effective steady-state concentration gradient. The logical flow of the calculations is outlined in figure 1.

2. Piecewise deterministic diffusion equation with age-structured switching

Consider the following diffusion equation for the density $u(x,t)$ of particles moving in a one-dimensional bounded domain with position $x \in [0,L]$ and time $t > 0$:

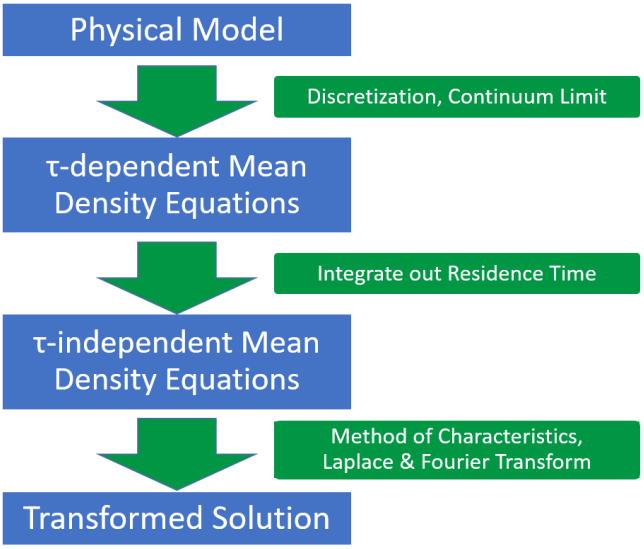

Figure 1. Outline of the steps in the calculation process for finding steady-state solutions to the first moment of equation (2.1).

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2}, \quad x \in [0, L], t > 0 \tag{2.1}$$

supplemented by the boundary conditions

$$u(0,t) = 0, \quad u(L,t) = \eta_0 > 0 \text{ for } n(t) = 0, \tag{2.2a}$$

$$u(0,t) = 0 \quad \chi\partial_x u(L,t) + (1-\chi)[u(L,t) - \eta_1] = 0 \text{ for } n(t) = 1, \tag{2.2b}$$

with $\chi = 0, 1$. Here $n(t) \in \{0, 1\}$ denotes the current state of a stochastic gate at the end $x = L$. If $n(t) = 0$ then the gate is open and the domain is in contact with a particle bath of fixed concentration η_0, whereas if $n(t) = 1$ then the gate is closed and particles are either partially exposed to the bath ($\chi = 0$, $\eta_1 < \eta_0$) or reflected ($\chi = 1$). In previous work [3, 18], we assumed that the state $n(t)$ of the gate evolves according to a two-state Markov chain: $0 \underset{\alpha_1}{\overset{\alpha_0}{\rightleftharpoons}} 1$. Let $P_n(t) = \sum_{m=0,1} \mathbb{P}[n(t) = n | n(0) = m]\, p^0_m$ be the probability distribution for the current state of the gate given that the initial state $n(0)$ is distributed according to p^0. We then have the master equation

$$\frac{\mathrm{d}P_n(t)}{\partial t} = \sum_{m=0,1} A_{nm} P_m(t) \tag{2.3}$$

where A is the matrix generator

$$A = \begin{bmatrix} -\alpha_0 & \alpha_1 \\ \alpha_0 & -\alpha_1 \end{bmatrix}. \tag{2.4}$$

The left nullspace of the matrix A is spanned by the vector $\psi = (1, 1)^\top$ and the right nullspace is spanned by

$$\rho \equiv \begin{pmatrix} \rho_0 \\ \rho_1 \end{pmatrix} = \frac{1}{\alpha_1 + \alpha_0} \begin{pmatrix} \alpha_1 \\ \alpha_0 \end{pmatrix}. \tag{2.5}$$

A simple application of the Perron–Frobenius theorem shows that the two state Markov process is ergodic with $\lim_{t\to\infty} P_n(t) = \rho_n$. One can view a solution of equation (2.1) up to some time t as determining the probability density $u(x,t)$ conditioned on a single realization $\{n(s), 0 \leqslant s < t\}$ of the stochastic gate. Thus the conditional probability density $u(x,t)$ can be interpreted as determining the density of multiple particles moving in the same random environment. Each realization of the gate will typically generate a different solution $u(x,t)$ so that $u(x,t)$ is a random field variable. Taking expectations with respect to these different realizations, conditioned on the current state of the gate, we define the first moments

$$V_n(x,t) = \mathbb{E}[u(x,t)1_{n(t)=n}], \quad n = 0, 1, \tag{2.6}$$

where $1_{n(t)=n}$ denotes the indicator function on the event $n(t) = n$. It can be shown using the method outlined in section 3 that V_n evolves according to the equations [3, 18]

$$\frac{\partial V_0}{\partial t} = D\frac{\partial^2 V_0}{\partial x^2} - \alpha_0 V_0 + \alpha_1 V_1, \tag{2.7a}$$

$$\frac{\partial V_1}{\partial t} = D\frac{\partial^2 V_1}{\partial x^2} + \alpha_0 V_0 - \alpha_1 V_1, \tag{2.7b}$$

with

$$V_0(0,t) = V_1(0,t) = 0,\ V_0(L,t) = \rho_0\eta_0,\ \chi\partial_x V_1(L,t) + (1-\chi)[V_1(L,t) - \rho_1\eta_1] = 0. \tag{2.8}$$

If $\chi = 0$ then the resulting steady-state solution for $V = V_0 + V_1$ is [4, 18]

$$V(x) = \frac{x}{L}[\rho_0\eta_0 + \rho_1\eta_1], \tag{2.9}$$

whereas for $\chi = 1$

$$V(x) = \frac{x}{L}\frac{\eta_0}{1 + (\rho_1/\rho_0)(\xi L)^{-1}\tanh(\xi L)}, \quad \xi = \sqrt{\alpha_0 + \alpha_1}. \tag{2.10}$$

In the latter case, although one has the expected linear gradient in concentration, the dependence of the slope on model parameters is non-trivial. However, one recovers the classical result in the fast switching limit $\xi \to \infty$:

$$V(x) = \frac{x}{L}\eta_0.$$

In this paper, we replace the simple two-state Markov chain by an age-structured model. That is, we introduce an additional time variable τ, which is the residence time between successive switches in the state of the gate, such that τ is reset to zero each time there is a state transition. We further assume that the switching rates depend on τ by setting $\alpha_1 = \alpha_1(\tau), \alpha_0 = \alpha_0(\tau)$. Let $\Lambda_n(t,\tau)$ denote the probability density that $n(t) = n$ and the last transition was at time $t - \tau$. We then have the age-structured master equation

$$\frac{\partial \Lambda_0(t,\tau)}{\partial t} + \frac{\partial \Lambda_0(t,\tau)}{\partial \tau} = -\alpha_0(\tau)\Lambda_0(t,\tau), \tag{2.11a}$$

$$\frac{\partial \Lambda_1(t,\tau)}{\partial t} + \frac{\partial \Lambda_1(t,\tau)}{\partial \tau} = -\alpha_1(\tau)\Lambda_1(t,\tau). \tag{2.11b}$$

This pair of equations is supplemented by the boundary conditions

$$\Lambda_0(t,0) = \int_0^{t^+} \alpha_1(\tau)\Lambda_1(t,\tau)\mathrm{d}\tau, \quad \Lambda_1(t,0) = \int_0^{t^+} \alpha_0(\tau)\Lambda_0(t,\tau)\mathrm{d}\tau, \quad (2.11c)$$

and the initial conditions $\Lambda_n(0,\tau) = \rho_n(\tau)\delta(\tau)$ with $\rho_n(\tau)$ given by equation (2.5) for τ-dependent $\alpha_n(\tau)$. Here t^+ mean the limit as $\epsilon \to 0$ of $t+\epsilon$, so that we capture the behavior of any singularities at $\tau = t^+$ resulting from the initial conditions. The marginal distribution $\lambda_n(t)$ is then obtained by integrating with respect to τ:

$$\lambda_n(t) = \int_0^{t^+} \Lambda_n(t,\tau)\mathrm{d}\tau. \quad (2.12)$$

One possible choice for age-dependent transition rates is (see [11–13])

$$\alpha_1(\tau) = \phi\frac{2\mu}{\tau_0+\tau}, \quad \alpha_0(\tau) = (1-\phi)\frac{2\mu}{\tau_0+\tau},$$

for $0 < \phi < 1$. Note that equations (2.11*a*)–(2.11*c*) are similar to the classical McKendrik-von Foerster equations in age-structured population dynamics [22, 25].

One question that quickly arises is what form the age-dependent rates $\alpha_1(\tau)$ and $\alpha_0(\tau)$ should take (we will focus on $\alpha_n(\tau) \equiv \alpha(\tau)$ for now). Define the random variable T to be the time until the next transition from $n=1$ to $n=0$ occurs. To investigate the relationship between T and $\alpha(\tau)$, we note that by definition of conditional probability, T, and $\alpha(\tau)$, we have that

$$\mathbb{P}(T > \tau + \Delta\tau | T > \tau) = \frac{\mathbb{P}(T > \tau + \Delta\tau)}{\mathbb{P}(T > \tau)} = 1 - \alpha(\tau)\Delta\tau + o(\Delta\tau).$$

Upon rearranging this equation, we have that

$$\frac{\mathbb{P}(T > \tau + \Delta\tau) - \mathbb{P}(T > \tau)}{\Delta\tau} = -\alpha(\tau)\mathbb{P}(T > \tau) + o(1).$$

Taking $\Delta\tau \to 0$ then yields that the survival probability $P_s(\tau) := \mathbb{P}(T > \tau)$ satisfies the ordinary differential equation (ODE)

$$\frac{\mathrm{d}P_s}{\mathrm{d}\tau} = -\alpha(\tau)P_s.$$

Hence,

$$P_s(\tau) = \mathcal{N}\exp\Big(-\int^{\tau} \alpha(s)\mathrm{d}s\Big),$$

where $\mathcal{N}$ is such that the probability density function (pdf) of T,

$$p(\tau) = -P_s'(\tau) = \mathcal{N}\alpha(\tau)\exp\Big(-\int^{\tau} \alpha(s)\mathrm{d}s\Big)$$

integrates to one, $\int_0^\infty p(\tau)\,\mathrm{d}\tau = 1$.

It follows that, given a survival probability distribution $P_s(\tau)$, we can construct the appropriate switching rate by

$$\alpha(\tau) = -\frac{P_s'(\tau)}{P_s(\tau)}. \quad (2.13)$$

As an informal example, consider the general class of transition rates given by $\alpha(\tau) = \mu(1+\tau)^k$. The resulting survival distribution is

$$P_s(\tau) = \mathcal{N} \exp\left(\frac{-\mu}{k+1}(1+\tau)^{k+1}\right) \text{ if } k \neq -1, \tag{2.14}$$

$$P_s(\tau) = \mathcal{N}\frac{1}{(1+\tau)^{\mu}} \text{ if } k = -1. \tag{2.15}$$

Note that if $k < -1$, we do not have a finite mean. Since in that case on average it takes an infinite amount of time for the system to change states, we will generally assume that our survival distribution has a finite mean.

3. First moment equations

We now extend our previous work on diffusion in switching environments to derive moment equations for the piecewise deterministic diffusion equation [3]. The first step is to spatially discretize the equation (2.1) using a finite-difference scheme. Introduce the lattice spacing a such that $(N+1)a = L$ for integer N, and let $u_j = u(aj)$ for $j = 0, \ldots, N+1$. We then obtain the piecewise deterministic ODE

$$\frac{\mathrm{d}u_i}{\mathrm{d}t} = \sum_{j=1}^{N} \Delta_{ij}^n u_j + \hat{\eta}_n \delta_{i,N}, \quad i = 1, \ldots, N, \quad n = 0, 1, \tag{3.1}$$

with

$$\hat{\eta}_n = \frac{\eta_0 D}{a^2}\delta_{n,0} + \frac{\eta_1 D}{a^2}\delta_{n,1}.$$

Away from the boundaries ($i \neq 1, N$), Δ_{ij}^n is given by the discrete Laplacian

$$\Delta_{ij}^n = \frac{D}{a^2}[\delta_{i,j+1} + \delta_{i,j-1} - 2\delta_{i,j}]. \tag{3.2a}$$

On the left-hand absorbing boundary we have $u_0 = 0$, whereas on the right-hand boundary we have

$$u_{N+1} = \eta_0 \text{ for } n = 0, \quad \chi(u_{N+1} - u_{N-1}) + (1-\chi)[u_{N+1} = \eta_1] = 0 \text{ for } n = 1.$$

These can be implemented by taking

$$\Delta_{1j}^n = \frac{D}{a^2}[\delta_{j,2} - 2\delta_{j,1}], \tag{3.2b}$$

$$\Delta_{Nj}^0 = \frac{D}{a^2}[\delta_{N-1,j} - 2\delta_{N,j}], \tag{3.2c}$$

$$\Delta_{Nj}^1 = \chi\frac{2D}{a^2}[\delta_{N-1,j} - \delta_{N,j}] + (1-\chi)\frac{D}{a^2}[\delta_{N-1,j} - 2\delta_{N,j}]. \tag{3.2d}$$

Let $\mathbf{u}(t) = (u_1(t), \ldots, u_N(t))$ and let $\tau(t) \geqslant 0$ be the time since the last switch

$$\tau(t) := \sup\{s < t : n(t) = n(t-s') \text{ for all } s' < s\}.$$

Introduce the probability density

$$\mathbb{P}\big\{\mathbf{u}(t)\in(\mathbf{u},\mathbf{u}+\mathrm{d}\mathbf{u}),n(t)=n,\tau(t)\in(\tau,\tau+\mathrm{d}\tau)\big\}=\mathcal{P}_n(\mathbf{u},t,\tau)\mathrm{d}\mathbf{u}\mathrm{d}\tau, \quad (3.3)$$

where we have dropped the explicit dependence on initial conditions. The probability density evolves according to the following differential Chapman–Kolmogorov (CK) [2] equation for the stochastic hybrid system (3.1):

$$\frac{\partial\mathcal{P}_n}{\partial t}+\frac{\partial\mathcal{P}_n}{\partial\tau}=-\sum_{i=1}^{N}\frac{\partial}{\partial u_i}\left[\left(\sum_{j=1}^{N}\Delta_{ij}^{n}u_j+\hat{\eta}_n\delta_{i,N}\right)\mathcal{P}_n(\mathbf{u},t,\tau)\right] -\alpha_n(\tau)\mathcal{P}_n(\mathbf{u},t,\tau). \quad (3.4)$$

Equation (3.4) is supplemented by the boundary conditions

$$\mathcal{P}_0(\mathbf{u},t,0)=\int_0^{t^+}\alpha_1(\tau)\mathcal{P}_1(\mathbf{u},t,\tau)\mathrm{d}\tau,\quad \mathcal{P}_1(\mathbf{u},t,0)=\int_0^{t^+}\alpha_0(\tau)\mathcal{P}_0(\mathbf{u},t,\tau)\mathrm{d}\tau \quad (3.5)$$

and the initial condition $\mathcal{P}_n(\mathbf{u},0,\tau)=\rho_n(0)\delta(\tau)f(\mathbf{u})$ with $\int f(\mathbf{u})\mathrm{d}\mathbf{u}=1$. Integrating equation (3.4) with respect to $\mathbf{u}$ and setting

$$\Lambda_n(t,\tau)=\int\mathcal{P}_n(\mathbf{u},t,\tau)\mathrm{d}\mathbf{u},$$

we recover (2.11*a*)–(2.11*c*).

Since the drift terms in the CK equation (3.4) are linear in the u_j, it follows that we can obtain a closed set of equations for the moments of $\mathcal{P}_n$. Introduce the first-order moments

$$V_{n,k}(t,\tau)=\int\mathcal{P}_n(\mathbf{u},t,\tau)u_k(t)\mathrm{d}\mathbf{u}\mathrm{d}\tau. \quad (3.6)$$

Multiplying both sides of the CK equation (3.4) by $u_k(t)$ and integrating with respect to $\mathbf{u}$ gives (after integrating by parts and using that $\mathcal{P}_n(\mathbf{u},t,\tau)\to 0$ as $\mathbf{u}\to\infty$ by the maximum principle)

$$\frac{\partial V_{n,k}}{\partial t}+\frac{\partial V_{n,k}}{\partial\tau}=\sum_{j=1}^{N}\Delta_{kj}^{n}V_{n,j}+\hat{\eta}_n\Lambda_n(t,\tau)\delta_{k,N}-\alpha_n(\tau)V_{n,k}(t,\tau). \quad (3.7)$$

If we now retake the continuum limit $a\to 0$, we obtain the moment equations for $V_n(x,t,\tau)$, namely,

$$\frac{\partial V_n(x,t,\tau)}{\partial t}+\frac{\partial V_n(x,t,\tau)}{\partial\tau}=D\frac{\partial^2V_n(x,t,\tau)}{\partial x^2}-\alpha_n(\tau)V_n(x,t,\tau). \quad (3.8)$$

This is supplemented by the boundary conditions

$$V_n(0,t,\tau)=0,\quad V_0(L,t,\tau)=\eta_0\Lambda_0(t,\tau), \quad (3.9a)$$

$$\chi\partial_xV_1(L,t,\tau)+(1-\chi)[V_1(L,t,\tau)-\eta_1\Lambda_1(t,\tau)]=0, \quad (3.9b)$$

with Λ_n evolving according to equations (2.11*a*) and (2.11*b*),

$$V_0(x,t,0)=\int_0^{t^+}\alpha_1(\tau)V_1(x,t,\tau)\mathrm{d}\tau,\quad V_1(x,t,0)=\int_0^{t^+}\alpha_0(\tau)V_0(x,t,\tau)\mathrm{d}\tau, \quad (3.9c)$$

and with the initial conditions

$$V_n(x,0,\tau) = V_n^{(0)}(x)\delta(\tau) \tag{3.9d}$$

for some initial spatial distribution $V_n^{(0)}(x)$.

4. Eliminating the residence time

In the previous section we derived equations for the τ-dependent first moments $V_n(x,t,\tau)$. The next step is to derive a non-Markovian master equation for the τ-independent moments

$$M_n(x,t) \equiv \int_0^{t^+} V_n(x,t,\tau)\mathrm{d}\tau, \tag{4.1a}$$

where we have integrated out the residence time τ. Note that we will need to be careful about the singularity at $\tau = t^+$ coming from the factor of $\delta(\tau)$ in the initial conditions. At this point it is convenient to define several additional variables. First, recall that the probability the gate is in state n at time t is given by

$$\lambda_n(t) \equiv \int_0^{t^+} \Lambda_n(t,\tau)\mathrm{d}\tau, \tag{4.1b}$$

analogous to the definition of $M_n(x,t)$. Now define

$$N_n(x,t) \equiv \int_0^{t^+} \alpha_n(\tau)V_n(x,t,\tau)\mathrm{d}\tau, \tag{4.1c}$$

$$r_n(t) \equiv \int_0^{t^+} \alpha_n(\tau)\Lambda_n(t,\tau)\mathrm{d}\tau. \tag{4.1d}$$

These new variables are integral terms describing the transfer of probability between $M_0(x,t)$, $M_1(x,t)$ and $\lambda_0(t), \lambda_1(t)$ respectively. We will proceed along analogous lines to Fedotov *et al* [12]. Given the boundary conditions (2.11*c*), (3.9*b*), and (3.9*c*) we also have to be able to solve for $N_n(x,t)$, as well as the variables $\lambda_n(t)$ and $r_n(t)$ through a similar process, since the marginal distribution $\Lambda_n(t,\tau)$, the τ-dependent probability density that the system is currently in state n at time t, is not known.

We can find the general form of the differential equation for $M_n(x,t)$ in a fairly straightforward manner. Integrating (3.8) from $\tau = 0$ to $\tau = t^+$, interchanging differentiation with integration, and using the fundamental theorem of calculus yields

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

Using the boundary condition $V_n(x,t,0) = \int_0^{t^+} \alpha_{1-n}(\tau)V_{1-n}(x,t,\tau)\mathrm{d}\tau = N_{1-n}(x,t)$, and the fact that $V_n(x,t,\sigma) = 0$ if $\sigma > t$, we obtain

$$\frac{\partial M_n(x,t)}{\partial t} = D\frac{\partial^2 M_n(x,t)}{\partial x^2} - N_n(x,t) + N_{1-n}(x,t), \tag{4.1e}$$

with boundary conditions

$$M_n(0,t) = 0, \quad M_0(L,t) = \eta_0\lambda_0(t), \tag{4.1f}$$

$$\chi\partial_x M_1(L,t) + (1-\chi)[M_1(L,t) - \eta_1\lambda_1(t)] = 0. \tag{4.1g}$$

In section 4.2 below, we use transform methods to rederive (4.1*e*) and write N_n in terms of M_n.

We note that the initial condition $V_n(x,0,\tau) = V_n^{(0)}(x)\delta(\tau)$ could be replaced by a smooth distribution of initial residence times $q_n(\tau)$, with $\int_0^\infty q_n(\tau)\mathrm{d}\tau = 1$. In this case, we integrate τ over $[0,\infty)$ in order to eliminate the residence time. This simplifies the derivation of equation (4.1*e*), since there is no longer a singularity at $\tau = t$, so that

$$\int_0^\infty \frac{\partial V_n(x,t,\tau)}{\partial \tau}\mathrm{d}\tau = -N_{1-n}(x,t).$$

For concreteness, we will use the point distribution $\delta(\tau)$ throughout the rest of the paper.

As in our previous studies, we are ultimately interested in the steady-state solution $M(x) = \lim_{t\to\infty}[M_0(x,t) + M_1(x,t)]$, under the assumption that the following limits exist:

$$\lambda_n^* = \lim_{t\to\infty} \lambda_n(t). \tag{4.2}$$

Adding the steady-state equations for $M_0(x)$ and $M_1(x)$ together yields

$$D\frac{\mathrm{d}^2 M(x)}{\mathrm{d}x^2} = 0, \tag{4.3}$$

which indicates that $M(x)$ is a straight line through the origin, $M(x) = Ax$, with A to be determined from the boundary conditions at $x = L$. In the Dirichlet–Dirichlet case ($\chi = 0$), one simply has

$$\lim_{t\to\infty} M(x,t) = \frac{x}{L}\lim_{t\to\infty}\left[\eta_0\lambda_0(t) + \eta_1\lambda_1(t)\right]. \tag{4.4}$$

Thus, it is only necessary to calculate $\lambda_n(t)$. The difficulty lies in the Dirichlet–Neumann case, where $M_1(L,t)$ is not known explicitly. This means that one has to solve equation (4.1*e*) 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. First, however, we show how to calculate $\lambda_n(t)$.

4.1. Calculation of $\lambda_n(t)$

The first step is to decompose the right-hand sides of equations (4.1*b*) and (4.1*d*) into two parts, one of which contains the singularity at $\tau = t^+$:

$$\lambda_n(t) = \int_0^{t^-} \Lambda_n(t,\tau)\mathrm{d}\tau + \int_{t^-}^{t^+} \Lambda_n(t,\tau)\mathrm{d}\tau \tag{4.5}$$

$$r_n(t) = \int_0^{t^-} \alpha_n(\tau)\Lambda_n(t,\tau)\mathrm{d}\tau + \int_{t^-}^{t^+} \alpha_n(\tau)\Lambda_n(t,\tau)\mathrm{d}\tau. \tag{4.6}$$

Note that $\lambda_n(t)$ is simply the probability that the system is in state n at time t. Using the method of characteristics (see figure 2) we can write

$$\Lambda_n(t,\tau) = \Lambda_n(t-\tau,0)\mathrm{e}^{-\int_0^\tau \alpha_n(t')\mathrm{d}t'} \quad \text{if} \quad t > \tau \tag{4.7a}$$

$$\Lambda_n(t,\tau) = \Lambda_n(0,\tau-t)\mathrm{e}^{-\int_{\tau-t}^\tau \alpha_n(t')\mathrm{d}t'} \quad \text{if} \quad t \leqslant \tau. \tag{4.7b}$$

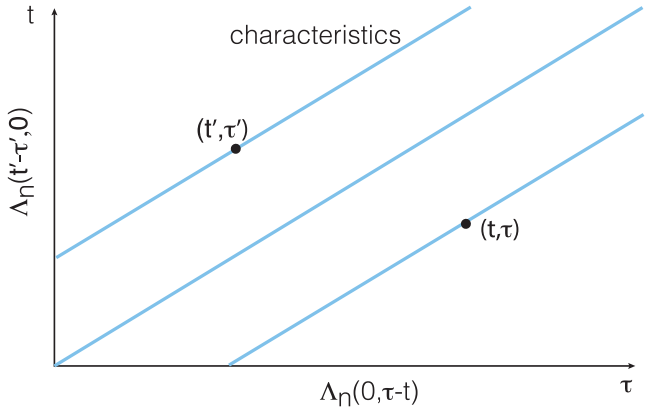

Figure 2. Characteristics used to determine $\Lambda_n(t,\tau)$ in terms of the initial data $\Lambda_n(t-\tau,0)$ for $t>\tau$ and $\Lambda_n(0,\tau-t)$ for $\tau>t$.

Note that

$$\Psi_n(\tau) \equiv \mathrm{e}^{-\int_0^\tau \alpha_n(t')\mathrm{d}t'} \tag{4.8}$$

is the survival probability that the system has not switched after residing in state n for time τ. We also define

$$\psi_n(\tau) \equiv \alpha_n(\tau)\mathrm{e}^{-\int_0^\tau \alpha_n(t')\mathrm{d}t'} = -\frac{\mathrm{d}\Psi_n(\tau)}{\mathrm{d}\tau}, \tag{4.9}$$

the pdf for the probability that the system has exited state n before reaching residence time τ. We can then write

$$\begin{aligned}\lambda_n(t) &= \int_0^{t^-} \Lambda_n(t-\tau,0)\Psi_n(\tau)\mathrm{d}\tau + \int_{t^-}^{t^+} \Lambda_n(0,\tau-t)\frac{\Psi_n(\tau)}{\Psi_n(\tau-t)}\mathrm{d}\tau\\ &= \int_0^{t} \Lambda_n(t-\tau,0)\Psi_n(\tau)\mathrm{d}\tau + \int_{t^-}^{t^+} \rho_n(0)\delta(\tau-t)\frac{\Psi_n(\tau)}{\Psi_n(\tau-t)}\mathrm{d}\tau\\ &= \Lambda_n(t,0)*\Psi_n(t) + \rho_n(0)\Psi_n(t)\\ &= (r_{1-n}*\Psi_n)(t) + \rho_n(0)\Psi_n(t),\end{aligned} \tag{4.10}$$

where we have used equation (2.11*c*). Similarly,

$$\begin{aligned}r_n(t) &= \int_0^{t^-} \Lambda_n(t-\tau,0)\psi_n(\tau)\mathrm{d}\tau + \int_{t^-}^{t^+} \alpha_n(\tau)\Lambda_n(t,\tau)\mathrm{d}\tau\\ &= (r_{1-n}*\psi_n)(t) + \rho_n(0)\psi_n(t).\end{aligned} \tag{4.11}$$

What is convenient about these forms is that we now have either linear terms or convolutions, making the Laplace transform ideal to use. Denoting $\mathcal{L}\{f(t)\} = \widetilde{f}(s)$, after applying the Laplace transform to both $r_n(t)$ and $\lambda_n(t)$, we arrive at the system of equations

$$\widetilde{\lambda}_n(s) = \widetilde{r}_{1-n}(s)\widetilde{\Psi}_n(s) + \rho_n(0)\widetilde{\Psi}_n(s) \tag{4.12a}$$

$$\widetilde{r}_n(s) = \widetilde{r}_{1-n}(s)\widetilde{\psi}_n(s) + \rho_n(0)\widetilde{\psi}_n(s). \tag{4.12b}$$

Solving (4.12*a*) for $\widetilde{r}_{1-n}(s)$ gives

$$\widetilde{r}_{1-n}(s) = \frac{\widetilde{\lambda}_n(s) - \rho_n(0)\widetilde{\Psi}_n(s)}{\widetilde{\Psi}_n(s)}.$$

This implies that

$$\widetilde{r}_n(s) = \frac{\widetilde{\psi}_n(s)}{\widetilde{\Psi}_n(s)}\big(\widetilde{\lambda}_n(s) - \rho_n(0)\widetilde{\Psi}_n(s)\big) + \rho_n(0)\widetilde{\psi}_n(s) = \frac{\widetilde{\psi}_n(s)}{\widetilde{\Psi}_n(s)}\widetilde{\lambda}_n(s),$$

and therefore

$$\widetilde{\lambda}_n(s) = \frac{\widetilde{\psi}_{1-n}(s)}{\widetilde{\Psi}_{1-n}(s)}\widetilde{\lambda}_{1-n}(s)\widetilde{\Psi}_n(s) + \rho_n(0)\widetilde{\Psi}_n(s).$$

Rewriting this as

$$\frac{\widetilde{\lambda}_n(s)}{\widetilde{\Psi}_n(s)} - \rho_n(0) = \frac{\widetilde{\psi}_{1-n}(s)}{\widetilde{\Psi}_{1-n}(s)}\widetilde{\lambda}_{1-n}(s),$$

we can subtract $(\widetilde{\psi}_n(s)/\widetilde{\Psi}_n(s))\widetilde{\lambda}_n(s)$ from both sides, yielding

$$\frac{\widetilde{\lambda}_n(s)[1-\widetilde{\psi}_n(s)]}{\widetilde{\Psi}_n(s)} - \rho_n(0) = \frac{\widetilde{\psi}_{1-n}(s)}{\widetilde{\Psi}_{1-n}(s)}\widetilde{\lambda}_{1-n}(s) - \frac{\widetilde{\psi}_n(s)}{\widetilde{\Psi}_n(s)}\widetilde{\lambda}_n(s).$$

Using the fact that $\widetilde{\psi}_n(s) = -s\widetilde{\Psi}_n(s) + 1$, we arrive at the equation

$$s\widetilde{\lambda}_n(s) - \rho_n(0) = \frac{\widetilde{\psi}_{1-n}(s)}{\widetilde{\Psi}_{1-n}(s)}\widetilde{\lambda}_{1-n}(s) - \frac{\widetilde{\psi}_n(s)}{\widetilde{\Psi}_n(s)}\widetilde{\lambda}_n(s) = \widetilde{r}_{n-1}(s) - \widetilde{r}_n(s). \quad (4.13)$$

Since $\mathcal{L}\{\dot{\lambda}_n(t)\} = s\widetilde{\lambda}_n(s) - \lambda_n(0) = s\widetilde{\lambda}_n(s) - \rho_n(0)$, we can convert back from the Laplace domain to the time domain to obtain the integro-differential equation

$$\frac{\mathrm{d}\lambda_n(t)}{\mathrm{d}t} = -r_n(t) + r_{1-n}(t), \quad (4.14)$$

where we have rewritten the transition rates as

$$r_n(t) = \int_0^{t^+} K_n(t-\tau)\lambda_n(\tau)\mathrm{d}\tau \quad (4.15)$$

with the integral kernel $K_n(t)$ defined by

$$K_n(t) = \mathcal{L}^{-1}\left\{\frac{\widetilde{\psi}_n(s)}{\widetilde{\Psi}_n(s)}\right\}. \quad (4.16)$$

In the Markovian case $\alpha_n(\tau) = \alpha_n$ constant, this formulation recovers the standard master equation for the two-state Markov chain. To see this, note that $\mathcal{L}\{\Psi(t)\} = \mathcal{L}\{\mathrm{e}^{-\alpha_n t}\} = (s+\alpha_n)^{-1}$, so the integral kernel is

$$K_n(t) = \mathcal{L}^{-1}\left\{\frac{1 - s\widetilde{\Psi}_n(s)}{\widetilde{\Psi}_n(s)}\right\} = \mathcal{L}^{-1}\{\alpha_n\} = \alpha_n\delta(t).$$

This means the rate functions are given by

$$r_n(t) = \int_0^{t^+} \alpha_n \delta(t-\tau)\lambda_n(\tau)\mathrm{d}\tau = \alpha_n \lambda_n(t),$$

and the resulting system of equations is

$$\frac{\mathrm{d}\lambda_n(t)}{\mathrm{d}t} = -\alpha_n\lambda_n(t) + \alpha_{1-n}\lambda_{1-n}(t), \quad n = 0, 1. \tag{4.17}$$

Our next intermediate step is to find the steady-state behavior of $\lambda_n(t)$ as $t \to \infty$. For now we will simply assume such a limit exists, i.e. the proportion of time spent in each discrete state approaches a constant value. Since the right hand side of (4.14) is non-autonomous, this is a non-trivial task. The main tool we use is the final value theorem of Laplace transforms. The idea is that, assuming $\lim_{t\to\infty} f(t)$ exists, we can use the identity

$$\int_0^\infty \mathrm{e}^{-st}\frac{\mathrm{d}f(t)}{\mathrm{d}t}\mathrm{d}t = sF(s) - f(0) \tag{4.18}$$

to equate $\lim_{s\to 0^+} sF(s) - f(0)$ with

$$\lim_{s\to 0^+}\int_0^\infty \mathrm{e}^{-st}\frac{\mathrm{d}f(t)}{\mathrm{d}t}\mathrm{d}t = \int_0^\infty \frac{\mathrm{d}f(t)}{\mathrm{d}t}\mathrm{d}t = \lim_{t\to\infty} f(t) - f(0).$$

Therefore, we have

$$\lim_{s\to 0^+} sF(s) = \lim_{t\to\infty} f(t). \tag{4.19}$$

In Laplace space, we can write the transform of the differential equations given by (4.14) as a system

$$\begin{pmatrix} s + \frac{\widetilde{\psi}_0(s)}{\widetilde{\Psi}_0(s)} & \frac{\widetilde{\psi}_1(s)}{\widetilde{\Psi}_1(s)} \\ \frac{\widetilde{\psi}_0(s)}{\widetilde{\Psi}_0(s)} & s + \frac{\widetilde{\psi}_1(s)}{\widetilde{\Psi}_1(s)} \end{pmatrix} \begin{pmatrix} \widetilde{\lambda}_0(s) \\ \widetilde{\lambda}_1(s) \end{pmatrix} = \begin{pmatrix} \rho_0(0) \\ \rho_1(0) \end{pmatrix}, \tag{4.20}$$

which we can use to solve for $s\widetilde{\lambda}_n(s)$, obtaining

$$\begin{pmatrix} s\widetilde{\lambda}_0(s) \\ s\widetilde{\lambda}_1(s) \end{pmatrix} = \frac{1}{s + \sum_{n=0,1}\frac{\widetilde{\psi}_n(s)}{\widetilde{\Psi}_n(s)}} \begin{pmatrix} s + \frac{\widetilde{\psi}_1(s)}{\widetilde{\Psi}_1(s)} & \frac{\widetilde{\psi}_1(s)}{\widetilde{\Psi}_1(s)} \\ \frac{\widetilde{\psi}_0(s)}{\widetilde{\Psi}_0(s)} & s + \frac{\widetilde{\psi}_0(s)}{\widetilde{\Psi}_0(s)} \end{pmatrix} \begin{pmatrix} \rho_0(0) \\ \rho_1(0) \end{pmatrix}. \tag{4.21}$$

Taking the limit $s \to 0^+$ yields the solution

$$\lim_{t\to\infty}\begin{pmatrix} \lambda_0(t) \\ \lambda_1(t) \end{pmatrix} = \lim_{s\to 0^+}\begin{pmatrix} s\widetilde{\lambda}_0(s) \\ s\widetilde{\lambda}_1(s) \end{pmatrix} = \begin{pmatrix} \frac{a_\lambda}{a_\lambda+b_\lambda} & \frac{a_\lambda}{a_\lambda+b_\lambda} \\ \frac{b_\lambda}{a_\lambda+b_\lambda} & \frac{b_\lambda}{a_\lambda+b_\lambda} \end{pmatrix}\begin{pmatrix} \rho_0(0) \\ \rho_1(0) \end{pmatrix} = \begin{pmatrix} \frac{a_\lambda}{a_\lambda+b_\lambda} \\ \frac{b_\lambda}{a_\lambda+b_\lambda} \end{pmatrix}, \tag{4.22}$$

where we have used $\rho_0(0) + \rho_1(0) = 1$, and defined

$$a_\lambda = \frac{\lim_{s\to 0^+}\widetilde{\psi}_1(s)}{\lim_{s\to 0^+}\widetilde{\Psi}_1(s)} = \frac{\int_0^\infty \psi_1(t)\mathrm{d}t}{\int_0^\infty \Psi_1(t)\mathrm{d}t} = \frac{1-\Psi_1(\infty)}{\int_0^\infty \Psi_1(t)\mathrm{d}t} = \frac{1}{\int_0^\infty \Psi_1(t)\mathrm{d}t}, \tag{4.23a}$$

$$b_\lambda = \frac{\lim_{s\to 0^+}\widetilde{\psi}_0(s)}{\lim_{s\to 0^+}\widetilde{\Psi}_0(s)} = \frac{\int_0^\infty \psi_0(t)\mathrm{d}t}{\int_0^\infty \Psi_0(t)\mathrm{d}t} = \frac{1-\Psi_0(\infty)}{\int_0^\infty \Psi_0(t)\mathrm{d}t} = \frac{1}{\int_0^\infty \Psi_0(t)\mathrm{d}t}, \tag{4.23b}$$

assuming the limit of each integral exists on its own. The last equalities follow from the fact that the survival probability approaches 0 as $t \to \infty$, assuming we have a reasonable holding

time distribution. Enforcing that $\psi_n(\tau)$ has a finite mean is one way of ensuring this. In the Markovian case, we arrive at $a_\lambda = \alpha_1$, $b_\lambda = \alpha_0$, which results in steady-state boundary conditions $\alpha_n/(\alpha_0 + \alpha_1) = \rho_n(0)$, identical to the Markovian boundary conditions one would normally obtain.

4.2. Calculation of $N_n(x,t)$

We now wish to perform a similar calculation to determine the functions $N_n(x,t)$ appearing in the PDE (4.1*e*) for $M_n(x,t)$. We will proceed by applying transform methods and the method of characteristics to the moment equation (3.8). First, note that we can take V_0, V_1 and $V = V_0 + V_1$ to be in the same Fourier space by taking them to be odd, periodic functions on the domain $[-L, L]$. These periodic functions will be discontinuous at $x = \pm L$. Introduce the sine series

$$V_n(x,t,\tau) = \sum_{l=1}^{\infty} \widehat{V}_{n,l}(t,\tau)\sin(l\pi x/L), \quad n = 0, 1, \tag{4.24}$$

with

$$\widehat{V}_{n,l}(t,\tau) = \frac{1}{L}\int_{-L}^{L} V_n(x,t,\tau)\sin(l\pi x/L)\mathrm{d}x. \tag{4.25}$$

Fourier transforming the moment equation (3.8) gives

$$\frac{\partial \widehat{V}_{n,l}}{\partial t} + \frac{\partial \widehat{V}_{n,l}}{\partial \tau} = -\left[Dk_l^2 + \alpha_n(\tau)\right]\widehat{V}_{n,l} + \frac{2Dk_l}{L}(-1)^{l+1}V_n(L,t,\tau), \tag{4.26}$$

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

$$\widehat{V}_{n,l}(0,\tau) = \widehat{V}_{n,l}^{(0)}\delta(\tau), \tag{4.27a}$$

$$\widehat{V}_{0,l}(t,0) = \int_0^{t^+} \alpha_1(\tau)V_{1,l}(t,\tau)\mathrm{d}\tau = \mathcal{N}_{1,l}(t), \tag{4.27b}$$

$$\widehat{V}_{1,l}(t,0) = \int_0^{t^+} \alpha_0(\tau)V_{0,l}(t,\tau)\mathrm{d}\tau = \mathcal{N}_{0,l}(t). \tag{4.27c}$$

Here $\mathcal{M}_{n,l}(t)$ and $\mathcal{N}_{n,l}(t)$ denote the sine transforms of $M(x,t)$ and $N(x,t)$. For the moment, 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 $\Lambda_n(t,\tau)$, see also figure 2. For $t > \tau$, we have

$$\widehat{V}_{n,l}(t,\tau) = \widehat{V}_{n,l}(t-\tau,0)\Psi_n(\tau)\mathrm{e}^{-Dk_l^2\tau} + B_{n,l}(t,\tau), \tag{4.28}$$

where

$$B_{n,l}(t,\tau) = \Psi_n(\tau)\mathrm{e}^{-Dk_l^2\tau}\frac{2Dk_l}{L}(-1)^{l+1}\int_0^{\tau}\frac{\mathrm{e}^{Dk_l^2\tau'}}{\Psi_n(\tau')}V_n(L,t-\tau+\tau',\tau')\mathrm{d}\tau'. \tag{4.29}$$

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

$$\widehat{V}_{n,l}(t,\tau) = \widehat{V}_{n,l}(0,\tau - t)\Psi_n(\tau)\mathrm{e}^{-Dk_l^2 t} + C_{n,l}(t,\tau), \tag{4.30}$$

where

$$C_{n,l}(t,\tau) = \Psi_n(\tau)\mathrm{e}^{-Dk_l^2 t}\frac{2k_l D}{L}(-1)^{l+1}\int_0^t \frac{\mathrm{e}^{Dk_l^2 t'}}{\Psi_n(t')}V_n(L,t',\tau - t + t')\mathrm{d}t'. \tag{4.31}$$

The functions $B_{n,l}(t,\tau)$ and $B_{n,l}(t,\tau)$ 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 equations (4.1*a*) and (4.1*c*) into two parts, one of which contains the singularity at $\tau = t^+$. After Fourier transforming we have

$$\mathcal{M}_{n,l}(t) = \int_0^{t^-} \widehat{V}_{n,l}(t,\tau)\mathrm{d}\tau + \int_{t^-}^{t^+} \widehat{V}_{n,l}(t,\tau)\mathrm{d}\tau \tag{4.32a}$$

$$\mathcal{N}_{n,l}(t) = \int_0^{t^-} \alpha_n(\tau)\widehat{V}_{n,l}(t,\tau)\mathrm{d}\tau + \int_{t^-}^{t^+} \alpha_n(\tau)\widehat{V}_{n,l}(t,\tau)\mathrm{d}\tau. \tag{4.32b}$$

Substituting the characteristic solution into this pair of equations and using equations (4.27*a*)–(4.27*c*), yields

$$\mathcal{M}_{n,l}(t) = (\mathcal{N}_{1-n,l} * \Phi_{n,l})(t) + \widehat{V}_{n,l}^{(0)}\Phi_{n,l}(t) + R_{n,l}(t), \tag{4.33a}$$

and

$$\mathcal{N}_{n,l}(t) = (\mathcal{N}_{1-n,l} * \phi_{n,l})(t) + \widehat{V}_{n,l}^{(0)}\phi_{n,l}(t) + S_{n,l}(t), \tag{4.33b}$$

where

$$R_{n,l}(t) = \int_0^{t^-} B_{n,l}(t,\tau)\mathrm{d}\tau + \int_{t^-}^{t^+} C_{n,l}(t,\tau)\mathrm{d}\tau, \tag{4.34a}$$

$$S_{n,l}(t) = \int_0^{t^-} \alpha_n(\tau)B_{n,l}(t,\tau)\mathrm{d}\tau + \int_{t^-}^{t^+} \alpha_n(\tau)C_{n,l}(t,\tau)\mathrm{d}\tau, \tag{4.34b}$$

and we have set

$$\Phi_{n,l}(t) = \Psi_n(t)\mathrm{e}^{-Dk_l^2 t}, \quad \phi_{n,l}(t) = \psi_n(t)\mathrm{e}^{-Dk_l^2 t}.$$

The terms R have a complicated form, but a simple interpretation. They describe the propagation of the memory of the gate at the right boundary into the interior of the domain along characteristics. Laplace transforming the above equations leads to the following algebraic system:

$$\widetilde{\mathcal{M}}_{n,l}(s) = \widetilde{\mathcal{N}}_{1-n,l}(s)\widetilde{\Psi}_n(s + Dk_l^2) + \widehat{V}_{n,l}^{(0)}\widetilde{\Psi}_n(s + Dk_l^2) + \widetilde{R}_{n,l}(s), \tag{4.35a}$$

$$\widetilde{\mathcal{N}}_{n,l}(s) = \widetilde{\mathcal{N}}_{1-n,l}(s)\widetilde{\psi}_n(s + Dk_l^2) + \widehat{V}_{n,l}^{(0)}\widetilde{\psi}_n(s + Dk_l^2) + \widetilde{S}_{n,l}(s), \tag{4.35b}$$

Finally, solving (4.35*a*) for $\widetilde{\mathcal{N}}_{1-n,l}(s)$ gives

$$\widetilde{\mathcal{N}}_{1-n,l}(s) = \frac{\widetilde{\mathcal{M}}_{n,l}(s) - V_{n,l}^{(0)}\widetilde{\Psi}_n(s + Dk_l^2) - \widetilde{R}_{n,l}(s)}{\widetilde{\Psi}_n(s + Dk_l^2)}.$$

Combining this with (4.35*b*), we have that

$$\begin{aligned}\widetilde{\mathcal{N}}_{n,l}(s) &= \frac{\widetilde{\psi}_n(s+Dk_l^2)}{\widetilde{\Psi}_n(s+Dk_l^2)}\big(\widetilde{\mathcal{M}}_{n,l}(s) - V_{n,l}^{(0)}\widetilde{\Psi}_n(s+Dk_l^2) - \widetilde{R}_{n,l}(s)\big) + V_{n,l}^{(0)}\widetilde{\psi}_n(s+Dk_l^2)\\ &\quad + \widetilde{S}_{n,l}(s)\\ &= \frac{\widetilde{\psi}_n(s+Dk_l^2)}{\widetilde{\Psi}_n(s+Dk_l^2)}\left[\widetilde{\mathcal{M}}_{n,l}(s) - \widetilde{R}_{n,l}(s)\right] + \widetilde{S}_{n,l}(s). \end{aligned} \tag{4.36}$$

Equation (4.36) 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 $x = L$.

It is also now possible to recover the PDE (4.1*e*). From equation (4.35*a*) we have

$$\begin{aligned}\widetilde{\mathcal{M}}_{n,l}(s) - \widetilde{R}_{n,l}(s) &= \frac{\widetilde{\psi}_{1-n}(s+Dk_l^2)}{\widetilde{\Psi}_{1-n}(s+Dk_l^2)}\left[\widetilde{\mathcal{M}}_{1-n,l}(s) - \widetilde{R}_{1-n,l}(s)\right]\widetilde{\Psi}_n(s+Dk_l^2)\\ &\quad + V_{n,l}^{(0)}\widetilde{\Psi}_n(s+Dk_l^2) + \widetilde{S}_{1-n,l}(s)\widetilde{\Psi}_n(s+Dk_l^2).\end{aligned}$$

Rewriting this as

$$\frac{\widetilde{\mathcal{M}}_{n,l}(s) - \widetilde{R}_{n,l}(s)}{\widetilde{\Psi}_n(s+Dk_l^2)} - V_{n,l}^{(0)} - \widetilde{S}_{1-n,l}(s) = \frac{\widetilde{\psi}_{1-n}(s+Dk_l^2)}{\widetilde{\Psi}_{1-n}(s+Dk_l^2)}\left[\widetilde{\mathcal{M}}_{1-n,l}(s) - \widetilde{R}_{1-n,l}(s)\right],$$

we can subtract

$$(\widetilde{\psi}_n(s+Dk_l^2)/\widetilde{\Psi}_n(s+Dk_l^2))[\widetilde{\mathcal{M}}_{n,l}(s) - \widetilde{R}_{n,l}(s)]$$

from both sides, yielding

$$\begin{aligned}\frac{[\widetilde{\mathcal{M}}_{n,l}(s) - \widetilde{R}_{n,l}(s)][1-\widetilde{\psi}_n(s+Dk_l^2)]}{\widetilde{\Psi}_n(s+Dk_l^2)} &= V_{n,l}^{(0)} + \widetilde{S}_{1-n,l}(s)\\ + \frac{\widetilde{\psi}_{1-n}(s+Dk_l^2)}{\widetilde{\Psi}_{1-n}(s+Dk_l^2)}[\widetilde{\mathcal{M}}_{1-n,l}(s) - \widetilde{R}_{1-n,l}(s)] &- \frac{\widetilde{\psi}_n(s+Dk_l^2)}{\widetilde{\Psi}_n(s+Dk_l^2)}[\widetilde{\mathcal{M}}_{n,l}(s) - \widetilde{R}_{n,l}(s)].\end{aligned}$$

Using the fact that $\widetilde{\psi}_n(s) = -s\widetilde{\Psi}_n(s) + 1$, we arrive at the equation

$$\begin{aligned}s[\widetilde{\mathcal{M}}_{n,l}(s) - \widetilde{R}_{n,l}(s)] - \widehat{V}_{n,l}^{(0)} - \widetilde{S}_{1-n,l}(s) &= -Dk_l^2[\widetilde{\mathcal{M}}_{n,l}(s) - \widetilde{R}_{n,l}(s)]\\ + \frac{\widetilde{\psi}_{1-n}(s+Dk_l^2)}{\widetilde{\Psi}_{1-n}(s+Dk_l^2)}[\widetilde{\mathcal{M}}_{1-n,l}(s) - \widetilde{R}_{1-n,l}(s)] &- \frac{\widetilde{\psi}_n(s+Dk_l^2)}{\widetilde{\Psi}_n(s+Dk_l^2)}[\widetilde{\mathcal{M}}_{n,l}(s) - \widetilde{R}_{n,l}(s)].\end{aligned}$$

Combining this with equation (4.36), we find

$$\begin{aligned}s\widetilde{\mathcal{M}}_{n,l}(s) - \widehat{V}_{n,l}^{(0)} &= -Dk_l^2\widetilde{\mathcal{M}}_{n,l}(s) + \widetilde{\mathcal{N}}_{1-n,l}(s) - \widetilde{\mathcal{N}}_{n,l}(s)\\ &\quad + [Dk_l^2 + s]\widetilde{R}_{n,l}(s) + \widetilde{S}_{n,l}(s).\end{aligned} \tag{4.37}$$

It is worth noting at this point that if the switching at the gate is given by an exponential distribution, which is memoryless, the dependence of the above equation on the memory terms $\widetilde{R}_{n,l}(s)$ and $\widetilde{S}_{n,l}(s)$ disappears, as the term $[Dk_l^2 + s]\widetilde{R}_{n,l}(s) + \widetilde{S}_{n,l}(s)$ cancels with the $\widetilde{R}_{n,l}(s)$ terms present in $\widetilde{\mathcal{N}}_{1-n,l}(s)$ and $\widetilde{\mathcal{N}}_{n,l}(s)$. Finally, inverting the Fourier–Laplace transform recovers equation (4.1*e*) with boundary conditions

$$M_n(0,t) = 0, \quad M_n(L,t) = F_n(t). \tag{4.38}$$

The Fourier–Laplace transform of the function $F_n(t)$ is given

$$\frac{2Dk_l}{L}(-1)^{l+1}\widetilde{\mathcal{F}}_n(s) = [Dk_l^2 + s]\widetilde{R}_{n,l}(s) + \widetilde{S}_{n,l}(s). \tag{4.39}$$

In order to determine the functions $\widetilde{R}_{n,l}(s)$ and $\widetilde{S}_{n,l}(s)$, we need to impose the explicit boundary conditions at $x = L$ for $B_{n,l}(t,\tau)$ and $C_{n,l}(t,\tau)$. The details of these calculations can be found in the appendix for both Dirchlet–Dirichlet ($\chi = 0$) and Dirchlet–Neumann ($\chi = 1$) boundary conditions. In the former case, we recover from equation (4.39) the expected result that $F_n(t) = \eta_n\lambda_n(t)$, which is a useful self-consistency check. The Dirchlet–Neumann case is more involved, since $F_0(t) = \eta_0\lambda_0(t)$ but $F_1(t)$ is unknown. The basic steps of the calculation are as follows. First, we express the steady-state version of $R_{n,l}(t)$ in terms of $F_n^* := \lim_{t\to\infty} F_n(t)$. Second, we express $\mathcal{M}_{0,l}$ and $\mathcal{N}_{n,l}, n = 0, 1$ in terms of $\mathcal{M}_{1,l}$ and F_n^*. It then follows that equation (A.8) can be used to determine $\mathcal{M}_{1,l}$ in terms of the coefficients F_n^*. Since $F_0^* = \eta_0\lambda_0^*$, there is only one unknown constant F_1^*. In the case of identical transition rates $\alpha_n(\tau) = \alpha_{1-n}(\tau) = \alpha(\tau)$, it is fairly straightforward to find a relatively compact form for the Fourier coefficients $\mathcal{M}_{1,l}$. In particular, after some algebra, we find that (see appendix),

$$\mathcal{M}_{1,l} = \frac{2}{Lk_l}(-1)^{l+1}\left[\frac{1}{\widetilde{\Psi}(0)}\frac{\widetilde{\Psi}(Dk_l^2)}{1+\widetilde{\psi}(Dk_l^2)}F_0^* + \left(1 - \frac{1}{\widetilde{\Psi}(0)}\frac{\widetilde{\Psi}(Dk_l^2)}{1+\widetilde{\psi}(Dk_l^2)}\right)F_1^*\right] \tag{4.40}$$

for Dirichlet–Neumann. Finally, the unknown constant $F_1^* = M_1(L)$ can be found by enforcing the Neumann boundary condition at $x = L$.

We are now in a position to determine the slope of the steady-state mean concentration for the Dirichlet–Neumann case. In order to calculate the spatial derivative of $M_1(x)$, it is convenient to be able to differentiate the Fourier series term by term. To do this, we must first homogenize the steady-state solution so that the values at $x = L$ and $x = -L$ are identical, then find the Fourier coefficients for the homogenized solution. This can be accomplished by simply subtracting the linear function xF_1^*/L from $M_1(x)$. Using linearity of Fourier series, the Fourier coefficients of $M_1^h(x) \equiv M_1(x) - xF_1^*/L$ are given by

$$\mathcal{M}_{1,l}^h = \frac{2}{Lk_l}(-1)^{l+1}\left[\frac{1}{\widetilde{\Psi}(0)}\frac{\widetilde{\Psi}(Dk_l^2)}{1+\widetilde{\psi}(Dk_l^2)}F_0^* - \frac{1}{\widetilde{\Psi}(0)}\frac{\widetilde{\Psi}(Dk_l^2)}{1+\widetilde{\psi}(Dk_l^2)}F_1^*\right]. \tag{4.41}$$

Setting

$$a_l = \frac{2}{Lk_l}(-1)^{l+1}\frac{1}{\widetilde{\Psi}(0)}\frac{\widetilde{\Psi}(Dk_l^2)}{1+\widetilde{\psi}(Dk_l^2)}, \tag{4.42}$$

we can then write

$$M_1(x) - \frac{x}{L}F_1^* = F_0^*\sum_{l=1}^{\infty} a_l\sin(k_lx) - F_1^*\sum_{l=1}^{\infty} a_l\sin(k_lx). \tag{4.43}$$

Taking derivatives and enforcing the Neumann boundary condition at $x = L$ gives the following expression for the unknown boundary value

$$M_1(L) = F_1^* = \frac{F_0^*\sum_{l=1}^{\infty}(-1)^l a_lk_l}{\sum_{l=1}^{\infty}(-1)^l a_lk_l - 1/L}, \quad k_l = \frac{\pi l}{L}. \tag{4.44}$$

Now $\lambda_0^* = 1/2$ since $\alpha_0 = \alpha_1$. Thus, setting

$$b_l = \frac{2\widetilde{\Psi}(Dk_l^2)}{1+\widetilde{\psi}(Dk_l^2)} = \frac{2(1-\widetilde{\psi}(Dk_l^2))}{Dk_l^2(1+\widetilde{\psi}(Dk_l^2))}, \tag{4.45}$$

we have that the slope of the steady state first moment $M(x)$ simplifies to

$$M'(x) = \frac{1}{L}(F_0^* + F_1^*) = \frac{\eta_0}{2L}\Big(1 + \frac{\sum_{l=1}^{\infty} b_l}{\sum_{l=1}^{\infty} b_l + \widetilde{\Psi}(0)}\Big),$$

where $\widetilde{\Psi}(0)$ is the mean time between switches.

5. Examples of rate functions

5.1. Markovian transition rates

The first example we will look at is the Markovian case $\alpha_n(\tau) = \alpha_n$. This has already been studied in [3, 18], and we will show our formulation yields the same results.

In the case of constant transition rate functions α_n, it is a straightforward calculation to show that

$$\widetilde{\Psi}_n(Dk^2) = \frac{1}{Dk_l^2 + \alpha_n}, \quad \frac{\widetilde{\psi}_n(Dk^2)}{\widetilde{\Psi}_n(Dk^2)} = \alpha_n, \quad \lambda_n = \frac{\alpha_{1-n}}{\alpha_0 + \alpha_1}.$$

Define $\xi = \sqrt{\alpha_0 + \alpha_1}$ and set $D = 1$. Substituting this into equation (A.8) yields

$$\begin{aligned} k_l^2 \mathcal{M}_{1,l} = \alpha_0 \left[\frac{2}{k_l L}(-1)^{l+1}\left[F_0^* + F_1^*\right] - \mathcal{M}_{1,l} - R_{0,l}\right] - k_l^2 R_{0,l} + \frac{2k_l}{L}(-1)^{l+1}F_0^* \\ - \alpha_1\left[\mathcal{M}_{1,l} - R_{1,l}\right] + k_l^2 R_{1,l} - \frac{2k_l}{L}(-1)^{l+1}F_1^* + \frac{2k_l}{L}(-1)^{l+1}F_1^*, \end{aligned} \tag{5.1}$$

where we have used

$$\mathcal{M}_{0,l} = \frac{2}{k_l L}(-1)^{l+1}\left[F_0^* + F_1^*\right] - \mathcal{M}_{1,l}. \tag{5.2}$$

After some algebra,

$$\begin{aligned} (k_l^2 + \xi^2)\mathcal{M}_{1,l} = \frac{2\alpha_0}{k_l L}(-1)^{l+1}\left[F_0^* + F_1^*\right] \\ - (\alpha_0 + k_l^2)R_{0,l} + (\alpha_1 + k_l^2)R_{1,l} + \frac{2k_l}{L}(-1)^{l+1}F_0^*. \end{aligned} \tag{5.3}$$

Equation (A.10) implies

$$R_{n,l} = \frac{1}{(\alpha_n + k_l^2)}\frac{2k_l}{L}(-1)^{l+1}F_n^* \tag{5.4}$$

so that

$$(k_l^2 + \xi^2)\mathcal{M}_{1,l} = \frac{2\alpha_0}{k_l L}(-1)^{l+1}\left[F_0^* + F_1^*\right] + \frac{2}{Lk_l}(-1)^{l+1}F_1^*. \tag{5.5}$$

From here we can find $M_{1,l}$ in terms of linear and hyperbolic functions. Enforcing $\partial_x M_{1,l} = 0$ at $x = L$ allows us to solve for the unknown value F_1^*. This yields

$$F_1^* = \lambda_1^* \lambda_0^* \eta_0 \frac{1 - (\xi L)^{-1} \tanh(\xi L)}{\lambda_0^* + \lambda_1^* (\xi L)^{-1} \tanh(\xi L)}, \tag{5.6}$$

with λ_0^*, λ_1^* defined according to equation (4.2).

Comparison with Monte Carlo simulations in figure 3(a), we can see that the numerical and analytical results match. For identical transition rates $\alpha_1 = \alpha_0 = \alpha$, we can also plot the slope of $M(x)$ as a function of α. The resulting curve approaches η/L as α grows, matching the result from taking a fast switching limit in (5.6), and drops exponentially to $\eta/2L$ as α grows (see figure 3(b)). This comes from the fact that as the switching rate slows down, the original switching system spends longer periods of time in the state $n = 1$, where $u(x, t) = 0$ is an exponentially attracting steady-sate solution. The contributions to the first moment then mainly come from the state $n = 0$ with a Dirichlet boundary condition $u(L, t) = \eta$, which is enforced half the time on average with identical switching rates.

5.2. Non-Markovian transition rates

We will illustrate the non-Markovian case using a gamma distribution

$$\psi(\tau) = \frac{1}{\Gamma(k)\beta^k} \tau^{k-1} \mathrm{e}^{-\frac{x}{\beta}} \tag{5.7}$$

for both transition rate probabilities. This distribution has the advantage that both the mean, given by $k\beta$, and the variance, given by $k\beta^2$, can both be easily controlled. In this case, the Laplace transform of $\psi(\tau)$ is given by

$$\widetilde{\psi}(s) = \frac{1}{(1 + \beta s)^k}. \tag{5.8}$$

Using the relation $\widetilde{\psi} = 1 - s\widetilde{\Psi}(s)$, we can find the Laplace transform of $\Psi(\tau)$ as

$$\widetilde{\Psi}(s) = \frac{(1 + \beta s)^k - 1}{s(1 + \beta s)^k}. \tag{5.9}$$

For this distribution, the value $\widetilde{\Psi}(0)$ does not exist, but $\lim_{s\to 0^+} \widetilde{\Psi}(s)$ does exist and is equal to $k\beta$, the first moment of the distribution $\psi(\tau)$. This is true in general for distributions with a finite mean, and we will interpret $\widetilde{\Psi}(0)$ as $\lim_{s\to 0^+} \widetilde{\Psi}(s) = \langle\psi\rangle$ as needed.

Comparing the analytical steady state $M(x)$ to Monte Carlo simulations using identical transition rates, we can see that they match to a high degree of accuracy, although the rate of convergence can be slow, see figure 4. Similar to the Markovian case, we can also see how the slope is predicted to change based on the the scale parameter β for fixed values of the shape parameter k, see figure 5. Note that as $k \to \infty$ the slope approaches

5.3. Sub-exponential transition rates with finite first moments

One advantage of our solution method is that it can predict what the first moment is even if the transition probability pdf $\psi(\tau)$ does not have finite variance. In these cases, it is not computationally feasible to calculate the mean steady-state using Monte Carlo simulations. However, from the analytical viewpoint developed in previous sections, as long as the mean time to transition to another state is finite, the calculations for $M(x)$ still hold and we can predict what the mean steady-state will be.

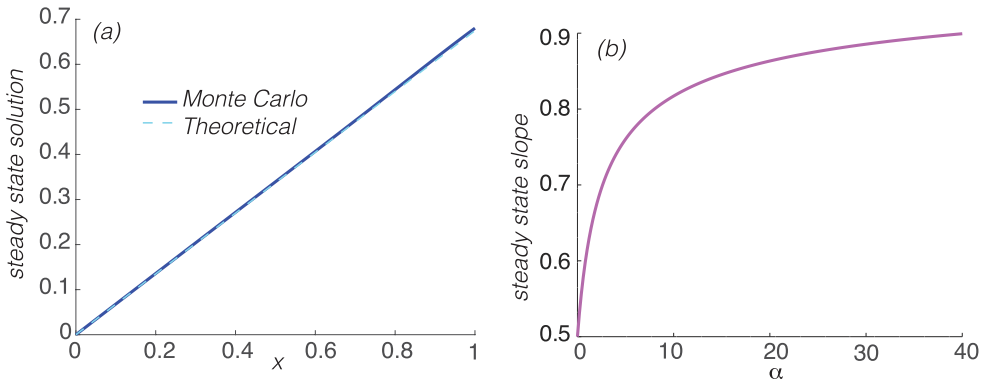

Figure 3. (a) Analytical and Monte Carlo steady-state solutions in the case of constant switching rates $\alpha_0 = \alpha_1 = \alpha$ with $\alpha = 2$. (b) Steady-state slope as a function of the constant switching rate α. We have set $\eta = L = 1$ for simplicity.

To illustrate this, consider a Pareto distribution given by

$$\psi(\tau) = \begin{cases} 0, & 0 \leqslant \tau < \tau_0 \\ \gamma \tau_0^{\gamma} / \tau^{\gamma+1}, & \tau \geqslant \tau_0 \end{cases} \tag{5.10}$$

with the shape parameter γ restricted to be in the interval $(1, 2)$ so that the mean of the distribution, given by $\gamma\tau_0/(\gamma - 1)$, is finite, but the variance is infinite. The Laplace transforms for both $\psi(\tau)$ and $\Psi(\tau)$ do not have closed forms, but can be expressed in terms of a generalized exponential integral

$$E_n(s) = \int_1^{\infty} \frac{\mathrm{e}^{-s\tau}}{\tau^n} \mathrm{d}\tau \tag{5.11}$$

or an incomplete gamma function

$$\Gamma(a, s) = \int_s^{\infty} \tau^{a-1} \mathrm{e}^{-\tau} \mathrm{d}\tau. \tag{5.12}$$

The results for the slope with various scale parameters τ_0 are shown in figure 6. There are several interesting features here. the slope seems to reach a saturating value, mimicking the behavior on the mean $\gamma\tau_0/(\gamma - 1)$ as γ approaches infinity. We also see that the curves approach a fast switching limit as τ_0 approaches 0 for for fixed values of γ, but all the curves approach 0.5 as γ goes to 1. A value of γ close to 1 can be interpreted as a slow switching limit, as the mean time for the system to switch states will be large. $M(x, t)$ will either be near identically 0 if $n = 1$, or be close to $\eta x/L = x$ if $n = 0$ for long periods of time, nearly wiping out any transitional behavior. Hence the average slope will approach 0.5 for our chosen parameter values $\eta = 1$ and $L = 1$.

5.4. Deterministic transition times

Our approach can also handle the case of deterministic switching times. In order for a switch out of state $n \in \{0, 1\}$ to occur at a fixed deterministic residence time $\tau_n > 0$, we take the rate functions to be delta functions, $\alpha_n = \delta(\tau - \tau_n)$. In this case we have $\Psi_n(\tau) = H(\tau_n - \tau)$, $\widetilde{\psi}_n(s) = \mathrm{e}^{-s\tau_n}$, and $\widetilde{\Psi}_n(s) = (1 - \mathrm{e}^{-s\tau_n})/s$. For simplicity, let $\tau_1 = \tau_0$, so that $\lambda_1^* = \lambda_0^* = 1/2$. Substituting this into (4.41) gives, after some simplification

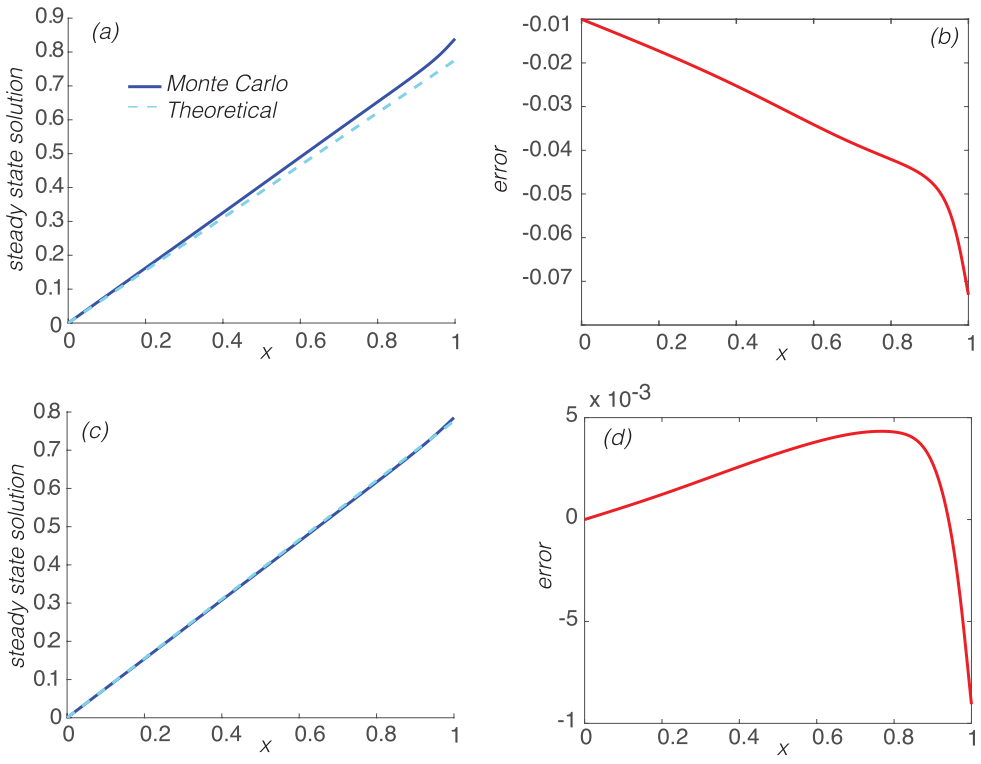

Figure 4. Comparison of the analytical and Monte Carlo steady-state solutions for the gamma distribution with (a) $t = 15$ and (c) $t = 1500$. The corresponding error differences are plotted as a function of x in (b) and (d), respectively. Parameters of the gamma distribution are $k = 2$, $\beta = 0.1$, and we have set $\eta = L = 1$.

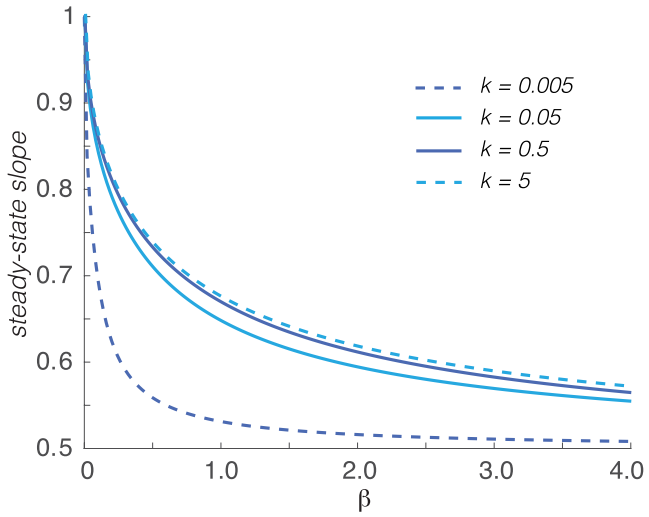

Figure 5. Steady-state slope for the gamma distribution as a function of β for various shape parameters: $k = 0.005$, $k = 0.05$, $k = 0.5$, and $k = 5$.

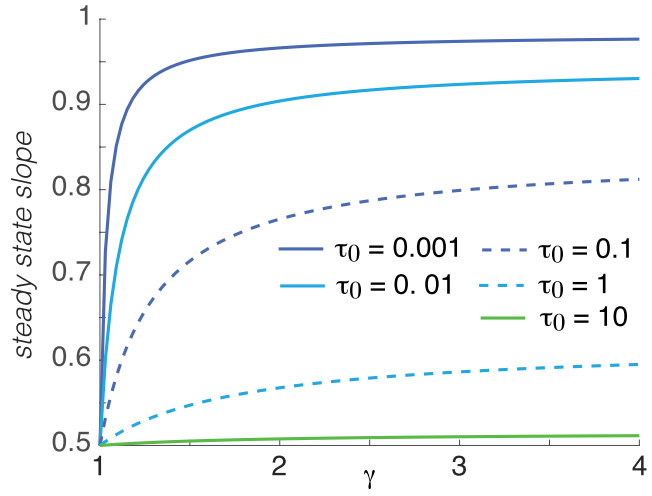

Figure 6. Steady-state slope for a switching rate based on a Pareto distribution with shape parameter γ varying from 1–4, and the scale parameter τ_0 set to 0.001, 0.01, 0.1, 1, and 10 (from top to bottom curves). Here we have set $L = \eta = 1$.

$$\mathcal{M}^h_{1,l} = \frac{2}{Lk_l}(-1)^{l+1}\frac{1-\mathrm{e}^{-Dk_l^2\tau_0}}{\tau_0 Dk_l^2(1+\mathrm{e}^{-Dk_l^2\tau_0})}[F_0^* - F_1^*]. \tag{5.13}$$

While using this to find an analytical expression for $M(x)$, we can compare the theoretical solution to Monte Carlo simulations (see figure 7(a)).

If we now take a fast switching limit $\tau_0 \to 0$, note that

$$\lim_{\tau_0\to 0}\mathcal{M}_{1,l} = \frac{1}{2}\mathcal{M}_l, \tag{5.14}$$

so we have the solution

$$\lim_{\tau_0\to 0} M_1(L) = \frac{1}{2}[F_0^* + \lim_{\tau_0\to 0} M_1(L)], \tag{5.15}$$

so $\lim_{\tau_0\to 0} M_1(L) = F_0^*$. The solution for the first moment is then

$$M(x) = \frac{\eta}{L}x. \tag{5.16}$$

This says that in the fast switching limit, the deterministic switching results in the system effectively being in an open state $n = 1$, which matches the known result that at rapidly switching system is equivalent to a system always in an open state. We can also see this from the plot of the slope as a a function of τ_0 shown in figure 7(b). As $\tau_0 \to 0$, the slope approaches $\eta/L = 1$.

5.5. Comparison of different switching time distributions

Finally, we compare the four different types of switching, Markovian, deterministic, gamma, and Pareto, by plotting the steady state slope, $M'(x)$, against the mean switching time. As is illustrated in figure 8(a), the deterministic and Markovian cases produce the most similar results, while the Pareto case has a more rapid change for small mean switching times. The

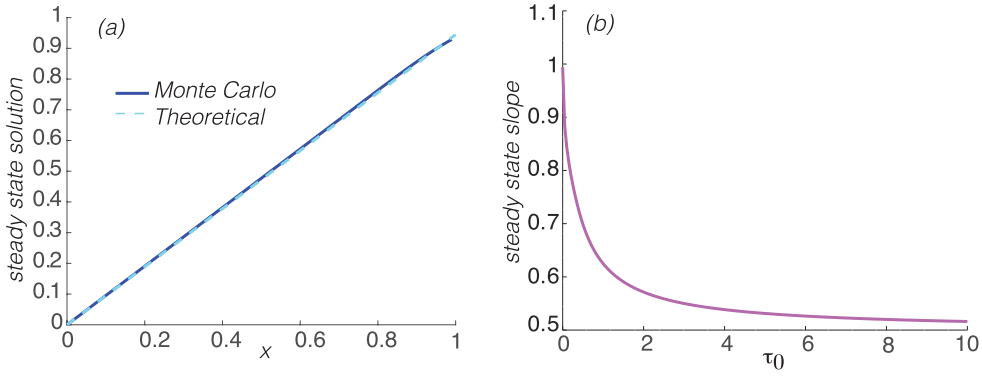

Figure 7. (a) Steady-state and Monte Carlo solution for deterministic switching occurring at time intervals $\tau_0 = 0.1$. (b) Steady-state slope as a function of switching interval τ_0.

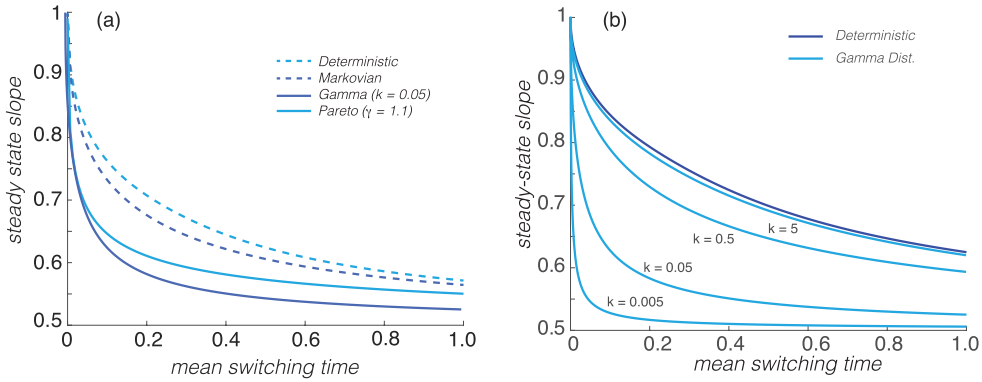

Figure 8. (a) Theoretical steady-state slope plotted against the mean switching time $\langle\psi\rangle$ for the four example distributions. For the gamma distribution and the Pareto distribution, we fix $k = 0.05$ and $\gamma = 1.1$ respectively. η and L are again set to unity. (b) Convergence of the gamma distribution curve to the deterministic curve in the large k limit.

most pronounced variation occurs for the gamma distribution, which takes the form of a sharp sigmoidal-like function. Nevertheless, all four distributions share the following features: a fast switching limit $(F_0^* + F_1^*)/L = 1$ as the mean switching time approaches 0, and a slow switching limit $(F_0^* + F_1^*)/L = 0.5$ as the mean time to transition to another state approaches infinity. Note that in the limits $k \to \infty$ and $\gamma \to \infty$, the gamma and Pareto distributions respectively approach the deterministic switching curve. This is illustrated in figure 8(b) for the gamma distribution. In addition, the sharper dependence on the mean switching time in the case of the gamma distribution can be explained as follows. Since the mean and variance of the gamma distribution are given by $k\beta$ and $k\beta^2$ respectively, if we fix the mean and take k small, since β is inversely proportional to k, β must be large. The variance is dependent on β^2, so the variance increases as k^{-2} when k approaches 0, leading to much greater variance in the

waiting times for the gate to switch states. As the support for the gamma distribution is $[0,\infty)$, this leads to longer switching times being more common. This phenomenon can be counteracted by taking the mean switching time to be very small, leading to the sharper dependence seen in figure 8.

6. Discussion

In this paper we have investigated the one-dimensional diffusion equation with randomly switching boundaries. In particular, we have extended the results of [3] for the slope of the steady-state solution in the Neumann–Dirichlet case to situations where there is an age-based memory to the switching rates, introduced through the residence time variable τ. Using the discretization approach from [3], we derive a system of linear PDEs for the moment equations. However, the introduction of age structure to the system brings with it several technicalities to deal with, namely a delta singularity in the initial conditions, and non-trivial integral boundary conditions at $\tau = 0$. To reformulate the problem without the residence time variable τ, we integrate out τ to obtain a system of integro-differential equations with integral terms depending on the τ-dependent moments V_n. To re-express these terms as function of the τ-independent moments M_n, we utilize transformation techniques. By sine-Fourier transforming the linear PDEs for V_n and using the method of characteristics on the resulting first-order system, we can rewrite M_n in terms of convolutions in time. Using the Laplace transform, we can solve the resulting algebraic system for the integral terms independent of V_n provided that the mean time to switch between states is finite.

We carry through with the calculations in transform space to find and solve transformed steady-state equations. Due to the switching between Neumann and Dirichlet boundary conditions, there is an unknown boundary value $M_1(L)$ that must be solved for by enforcing the no-flux boundary condition at $x = L$. The final results from the analysis match numerical results from Monte Carlo simulations in all the cases that we tested.

Due to the relationship between the transition rates α_n and the survival distribution $\Psi(\tau)$, age structured switching can be used to model phenomena where the switching is observed to follow a non-exponential distribution, even if the source of this age-structure is not explicitly known. One particularly relevant example concerns the non-exponential residence time intervals observed in ion channel gating dynamics, see [14] and references therein. Although a nonexponential distribution could be approximately fitted by a sum of exponentials, often the number of required terms can be large and may change with experimental conditions. This has motivated the development of anomalous diffusion-like models of ion-channel gating.

Finally, another natural question is whether or not our analysis can be extended to the case where the switching rates depend on some spatial structure or on the density u. Specific cases have been investigated already [12, 13], but a general approach seems at the very least to be extremely technical.

Acknowledgments

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Appendix

A.1. Case $\chi = 0$

As a self-consistency check, we show that equation (4.39) yields $F_n(t) = \eta_n \lambda_n(t)$ when $\chi = 0$. The explicit boundary conditions for V_n are $V_n(L,t,\tau) = \eta_n \Lambda_n(t,\tau)$ with $\Lambda_n(t,\tau)$ having the characteristic solutions (4.7*a*) and (4.7*b*). Substituting these solutions into equations (4.29) and (4.31), respectively, gives

$$B_{n,l}(t,\tau) = \Psi_n(\tau)\frac{2k_l D\eta_n}{L}(-1)^{l+1}\Lambda_n(t-\tau,0)\frac{1-\mathrm{e}^{-Dk_l^2\tau}}{Dk_l^2}, \quad t>\tau \tag{A.1}$$

and

$$C_{n,l}(t,\tau) = \frac{2k_l\eta_n D}{L}(-1)^{l+1}\rho_n(0)\Psi_n(t)\left(1-\mathrm{e}^{-Dk_l^2 t}\right)\delta(\tau-t), \quad \tau\in[t^-,t^+]. \tag{A.2}$$

It follows that

$$\int_0^{t^-} B_{n,l}(t,\tau)\mathrm{d}\tau = \frac{2\eta_n}{Lk_l}(-1)^{l+1}(r_{1-n}*[\Psi_n-\Phi_{n,l}])(t),$$
$$\int_0^{t^-} \alpha(\tau)B_{n,l}(t,\tau)\mathrm{d}\tau = \frac{2\eta_n}{Lk_l}(-1)^{l+1}(r_{1-n}*[\psi_n-\phi_{n,l}])(t),$$

$$\int_{t^-}^{t^+} C_{n,l}(t,\tau)\mathrm{d}\tau = \frac{2\eta_n}{Lk_l}(-1)^{l+1}\rho_n(0)\Psi_n(t)\left(1-\mathrm{e}^{-Dk_l^2 t}\right),$$
$$\int_{t^-}^{t^+} \alpha_n(\tau)C_{n,l}(t,\tau)\mathrm{d}\tau = \frac{2\eta_n}{Lk_l}(-1)^{l+1}\rho_n(0)\psi_n(t)\left(1-\mathrm{e}^{-Dk_l^2 t}\right).$$

We have used the fact that $r_{1-n}(t) = \Lambda_n(t,0)$, which follows from (2.11*c*) and (4.1*d*) The Laplace transforms of equations (4.35*a*) and (4.35*b*) thus yield

$$\widetilde{R}_{n,l}(s) = \frac{2\eta_n}{Lk_l}(-1)^{l+1}\left[\widetilde{r}_{1-n}(s)+\rho_n(0)\right]\left[\widetilde{\Psi}_n(s)-\widetilde{\Psi}_n(s+Dk_l^2)\right], \tag{A.3}$$

and

$$\begin{aligned}\widetilde{S}_{n,l}(s) &= \frac{2\eta_n}{Lk_l}(-1)^{l+1}\left[\widetilde{r}_{1-n}(s)+\rho_n(0)\right]\left[\widetilde{\psi}_n(s)-\widetilde{\psi}_n(s+Dk_l^2)\right]\\ &= -s\widetilde{R}_{n,l}(s)+Dk_l^2\frac{2\eta_n}{Lk_l}(-1)^{l+1}\left[\widetilde{r}_{1-n}(s)+\rho_n(0)\right]\widetilde{\Psi}_n(s+Dk_l^2).\end{aligned} \tag{A.4}$$

Again we have used $\widetilde{\psi}_n(s) = -s\widetilde{\Psi}_n(s)+1$. Equations (4.12*a*), (A.3) and (A.4) imply that

$$\begin{aligned}[Dk_l^2+s]\widetilde{R}_{n,l}(s)+\widetilde{S}_{n,l}(s) &= \frac{2Dk_l\eta_n}{L}(-1)^{l+1}\left[\widetilde{r}_{1-n}(s)+\rho_n(0)\right]\widetilde{\Psi}_n(s)\\ &= \frac{2Dk_l}{L}(-1)^{l+1}\eta_n\widetilde{\lambda}_n(s).\end{aligned}$$

A.2. Case $\chi = 1$

In this case we do not have an explicit formula for $F_1(t)$, since we have to determine $V_1(L,t,\tau)$ given that $\partial_x V_1(L,t,\tau) = 0$. (The analysis for $\chi = 0$ carries over for $n = 0$, that is, $F_0(t) = \eta_0\lambda_0(t)$.) The steady-state version of equation (4.1*e*) takes the form

$$0 = D\frac{d^2M_n(x)}{\partial x^2} - N_n(x) + N_{1-n}(x), \tag{A.5}$$

with boundary conditions

$$M_n(0) = 0, \quad M_0(L) = \eta_0\lambda_0^*, \quad M_1(L) = F_1^*, \quad \partial_x M_1(L) = 0, \tag{A.6}$$

assuming the following limits exist

$$N_n(x) = \lim_{t\to\infty} N_n(x,t), \quad F_1^* = \lim_{t\to\infty} F_1(t).$$

Adding equation (A.5) for $n = 0, 1$, the straight line solution for $M(x) = M_0(x) + M_1(x)$ is given by

$$M(x) = \frac{x}{L}\left[\eta_0\lambda_0^* + F_1^*\right]. \tag{A.7}$$

In Fourier space, we have

$$0 = -Dk_l^2\mathcal{M}_{1,l} + \mathcal{N}_{0,l} - \mathcal{N}_{1,l} + \frac{2Dk_l}{L}(-1)^{l+1}F_1^*, \tag{A.8}$$

and

$$\mathcal{M}_l = \mathcal{M}_{0,l} + \mathcal{M}_{1,l} = \frac{2}{k_l L}(-1)^{l+1}\left[\eta_0\lambda_0^* + F_1^*\right]. \tag{A.9}$$

Adapting the analysis of the $\chi = 0$ case, we require

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

with $F_0(t) = \eta_0\lambda_0(t)$ and $\lim_{s\to 0^+} s\Delta_{1,l}(s) = 0$. The intuition here is that the method of characteristics propagates information about the value of V_n at the boundary directly, with information about $\partial_x V_n$ being included indirectly through V_n. This suggests that the form for $R_{1,l}$ should match the form for $R_{0,l}$. It follows that

$$\begin{aligned} R_{n,l} &= \frac{2}{Lk_l}(-1)^{l+1}\lim_{s\to 0^+} s[\widetilde{\mathcal{F}}_n(s) + \Delta_{1,l}(s)\delta_{n,1}]\left[1 - \frac{\widetilde{\Psi}_n(s+Dk_l^2)}{\widetilde{\Psi}_n(s)}\right], \\ &= \frac{2}{Lk_l}(-1)^{l+1}\left[1 - \frac{\widetilde{\Psi}_n(Dk_l^2)}{\widetilde{\Psi}_n(0)}\right]F_n^*. \end{aligned} \tag{A.10}$$

Similarly, from equation (4.39)

$$\begin{aligned} Dk_l^2R_{n,l} + S_{n,l} &= \lim_{s\to 0^+} s\left[[Dk_l^2 + s]\widetilde{R}_{n,l}(s) + \widetilde{S}_{n,l}(s)\right], \\ &= \frac{2Dk_l}{L}(-1)^{l+1}F_n^*, \end{aligned} \tag{A.11}$$

and

$$\mathcal{N}_{n,l} = \lim_{s\to 0^+} s\left[\frac{\widetilde{\psi}_n(s+Dk_l^2)}{\widetilde{\Psi}_n(s+Dk_l^2)}\left[\widetilde{\mathcal{M}}_{n,l}(s)-\widetilde{R}_{n,l}(s)\right]+\widetilde{S}_{n,l}(s)\right]$$

$$= \frac{\widetilde{\psi}_n(Dk_l^2)}{\widetilde{\Psi}_n(Dk_l^2)}\left[\mathcal{M}_{n,l}-R_{n,l}\right]+S_{n,l} \tag{A.12}$$

$$= \frac{\widetilde{\psi}_n(Dk_l^2)}{\widetilde{\Psi}_n(Dk_l^2)}\left[\mathcal{M}_{n,l}-R_{n,l}\right]-Dk_l^2R_{n,l}+\frac{2Dk_l}{L}(-1)^{l+1}F_n^* \tag{A.13}$$

$$= \frac{\widetilde{\psi}_n(Dk_l^2)}{\widetilde{\Psi}_n(Dk_l^2)}\mathcal{M}_{n,l}-\frac{1}{\widetilde{\Psi}_n(Dk_l^2)}R_{n,l}+\frac{2Dk_l}{L}(-1)^{l+1}F_n^*, \tag{A.14}$$

where the last equality follows from the relation

$$\frac{\widetilde{\psi}_n(Dk_l^2)}{\widetilde{\Psi}_n(Dk_l^2)}+Dk_l^2=\frac{1}{\widetilde{\Psi}_n(Dk_l^2)}.$$

We now make a number of observations. First $R_{n,l}$ can be expressed in terms of F_n^*. Second, we can express $\mathcal{M}_{0,l}$, and $\mathcal{N}_{n,l}, n=0,1$ in terms of $\mathcal{M}_{1,l}$ and F_n^*. It follows that equation (A.8) can be used to determine $\mathcal{M}_{1,l}$ in terms of the coefficients F_n^*. Since $F_0^*=\eta_0\lambda_0^*$, there is only one unknown constant F_1^*. The latter can be determined by imposing the remaining boundary condition $\partial_x M_1(L)=0$.

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