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Residence times of a Brownian particle with temporal heterogeneity

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Abstract

We consider a diffusing particle that randomly switches conformational state. Motivated by various scenarios in cell biology, we suppose that (a) the diffusion coefficient depends on the conformational state and/or (b) the particle can only pass through a series of gates in the domain when it is in a particular conformational state. We develop probabilistic methods to analyze this case of diffusion with temporal heterogeneity, and use these methods to calculate the expected residence time in portions of the domain before absorption at a boundary. We find several new phenomena not seen in recent studies of diffusion with spatial heterogeneity, some of which are counterintuitive. In particular, the expected residence times can be non-monotonic functions of (i) the initial distance from the absorbing boundary and (ii) the diffusion coefficients. We focus on one-dimensional intervals, but show how the analysis can be extended to spherically symmetric d-dimensional domains.

Keywords: Brownian motion, residence times, stochastic gates, first passage times, temporal heterogenieity

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

1. Introduction

A fundamental quantity in the mathematical theory of random walks and diffusion processes is the *occupation time* [16, 18], which was originally defined as the time spent by a Brownian particle in $\mathbb{R}^+ = [0, \infty)$ within a time window of size t. That is, given the Brownian motion $X(t) \in \mathbb{R}$, the occupation time T is

$$T := \int_0^t \Theta(X(\tau))\mathrm{d}\tau, \tag{1.1}$$

where $\Theta(X)$ denotes the Heaviside function. The occupation time T is an example of a Brownian functional. Since $X(t)$, $t \geqslant 0$, is a Wiener process, it follows that each realization of a Brownian path will typically yield a different value of T, which means that T will be distributed according to some probability density $P(T,t|x_0,0)$ for $X(0)=x_0$. The statistical properties of a Brownian functional can be analyzed using path integrals, and leads to the well-known *Feynman–Kac* formula [17]. For a general review of Brownian functionals and their applications, see [19]. An immediate generalization of equation (1.1) is to take

$$T := \int_0^t I_V(X(\tau))\mathrm{d}\tau, \tag{1.2}$$

where $X(t) \in \mathbb{R}^d$ is a continuous stochastic process and $I_V(x)$ denotes the indicator function of the set $V \subset \mathbb{R}^d$, that is, $I_V(x)=1$ if $x \in V$ and is zero otherwise. (Note that for one-dimensional (1D) motion, $\Theta(x)=I_{\mathbb{R}+}(x)$.) More recently, occupation times have figured prominently in a variety of physical applications under the alternative name of *residence times*. Examples include the non-equilibrium dynamics of coarsening systems [11, 20], ergodicity properties of anomalous diffusion [10, 21], simple models of blinking quantum dots [22], fluorescent imaging [1], and branching processes [12]. Since a residence time concerns the amount of time that a Brownian particle spends in some bounded or partially bounded domain $\mathcal{M} \subset \mathbb{R}^d$, a natural extension is to replace the upper limit t by a stopping time such as the first passage time (FPT) to reach a section of the boundary $\partial\mathcal{M}$. This type of residence time has recently played an important role in the calculation of mean first-passage times (MFPTs) in spatially heterogeneous media [9, 23, 24].

In this paper we use probabilistic methods (conditional expectations and the strong Markov property) to determine the stopped residence times of a Brownian particle in a bounded domain with temporal rather than spatial heterogeneity. The introduction of temporal heterogeneity is motivated by the idea that macromolecules in cell biology often switch between different conformational states [2]. For simplicity, we will assume that a particle can randomly switch between two conformational states labeled $n=0$, 1 and that this switch has two possible effects: (i) the diffusion coefficient depends on the state n and (ii) there are pores separating different spatial domains and the particle can only pass through a pore when in the state $n=0$, say. Thus the pore acts like a stochastic gap junction [6, 7]. These two cases are illustrated in figure 1. The analysis of residence times with a switching diffusion coefficient is presented in section 2, and the extension to stochastically-gated residence times is presented in section 3. In particular, we show how temporal heterogeneity can lead to counterintuitive behaviors, such as the non-monotonic dependence of expected residence times on the initial distance from an absorbing boundary and on the diffusion coefficient.

2. Residence times without gating

2.1. Brownian particle with temporal heterogeneity

Consider a Brownian particle diffusing in the one-dimensional (1D) domain of length L shown in figure 2. The domain is partitioned into cells of size l, $ml=L$, with a pore or gate at each junction $x=kl$, $k=1,\ldots(m-1)l$. Suppose that the particle switches between two conformational states labelled $n=0,1$ such that $n(t)\in\{0,1\}$ evolves according to a two-state Markov chain, $0 \underset{\alpha}{\overset{\beta}{\rightleftharpoons}} 1$, with the matrix generator

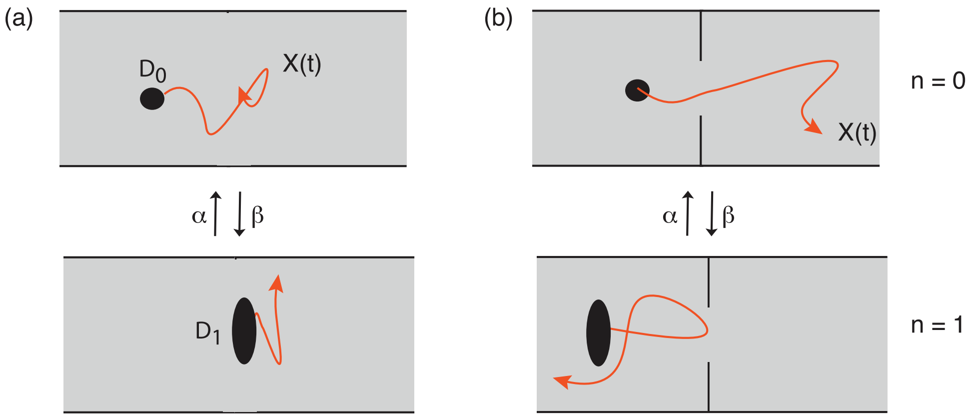

Figure 1. Schematic diagram of two possible trajectories for a Brownian particle that randomly switches between two conformational states $n = 0,\ 1$ according to a two-state Markov chain with transition rates α, β (temporal heterogeneity). (a) Switching between different diffusion coefficients D_0, D_1. (b) Brownian particle can only pass through a pore when in the state $n = 0$.

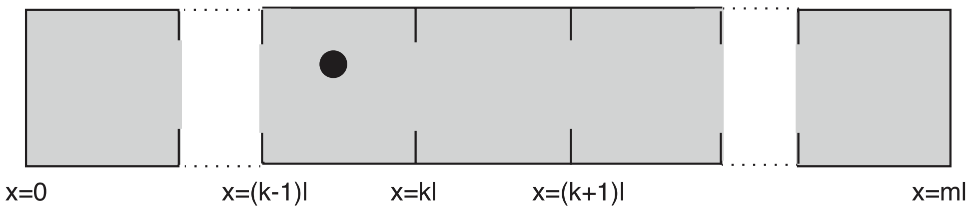

Figure 2. One-dimensional domain of length L partitioned into m cells of size l with gap junctions at the interior points $x = a_k = kl$, $k = 1, m - 1$.

$$\mathbf{A} = \begin{pmatrix} -\beta & \alpha \\ \beta & -\alpha \end{pmatrix}. \tag{2.1}$$

We assume that the two conformational states have distinct diffusion coefficients D_n, $n = 0, 1$ as illustrated in figure 1(a). We then distinguish between two scenarios.

(i) *Ungated*: the particle can pass through the pores in both conformational states so the cell junctions have no effect.
(ii) *Gated*: the particle can only pass through a pore in conformational state $n = 0$, see figure 1(b).

In this section we focus on the ungated case, and consider the effects of gating in section 3. Let $X(t)$ be the position of the particle at time t, which evolves according to the piecewise stochastic differential equation (SDE)

$$\mathrm{d}X(t) = \sqrt{2D_n}\,\mathrm{d}W(t), \tag{2.2}$$

when $n(t) = n \in \{0, 1\}$. Here $W(t)$ is a Wiener process with $\langle \mathrm{d}W(t)\rangle = 0$ and $\langle \mathrm{d}W(t)\mathrm{d}W(t')\rangle = \delta(t - t')\mathrm{d}t\mathrm{d}t'$.

Assuming the initial conditions $X(0) = x_0, n(0) = n_0$, we introduce the probability density $p_n(x,t|x_0,n_0,0)$ with

$$\mathbb{P}\{X(t) \in (x, x+\mathrm{d}x),\ n(t) = n|x_0, n_0\} = p_n(x,t|x_0,n_0,0)\mathrm{d}x.$$

It follows that p_n evolves according to the forward differential CK equation (dropping the explicit dependence on initial conditions) [2, 14]

$$\frac{\partial p_n}{\partial t} = D_n \frac{\partial^2 p_n(x,t)}{\partial x^2} + \sum_{m=0,1} A_{nm} p_m(x,t), \quad n = 0, 1. \tag{2.3}$$

Now suppose that there is an absorbing boundary condition at $x = 0$ and a reflecting boundary condition at $x = L$:

$$p_n(0,t) = 0, \quad \frac{\partial p_n(L,t)}{\partial x} = 0. \tag{2.4}$$

Given the first passage time

$$\mathcal{T} := \inf\{t > 0 : X(t) = 0\}, \tag{2.5}$$

we define the (stopped) residence time in the interval (a_k, a_{k+1}) according to

$$\mathcal{T}_k := \int_0^{\mathcal{T}} I_{(a_k,a_{k+1})}(X(t))\mathrm{d}t, \quad k = 0, \ldots, m-1. \tag{2.6}$$

Note that $\sum_{k=0}^{m-1} \mathcal{T}_k = \mathcal{T}$ almost surely.

In this paper we are interested in calculating the mean residence times $\tau_k^m(x_0)$, where

$$\tau_k^m(x_0) = \mathbb{E}_{x_0,m}[\mathcal{T}_k], \tag{2.7}$$

with $\mathcal{T}_k$ the residence time in the interval (a_k, a_{k+1}) and $\mathbb{E}_{x_0,m}$ denotes expectation with respect to the stochastic process conditioned on $X(0) = x_0$ and $n(0) = m$. Given the solution $p_n(x,t|x_0,m,0)$ to the CK equation (2.3), we have

$$\tau_k^m(x_0) = \sum_{n=0,1} \int_{a_k}^{a_{k+1}} \mathrm{d}x \int_0^\infty \mathrm{d}t\, p_n(x,t|x_0,m,0). \tag{2.8}$$

Setting $q_m(x_0,t) = \sum_{n=0,1} p_n(x,t|x_0,m,0)$, the backward CK equation takes the form

$$\frac{\partial q_m}{\partial t} = D_m \frac{\partial^2 q_m(x_0,t)}{\partial x_0^2} + \sum_{n=0,1} A_{mn}^\top q_n(x_0,t). \tag{2.9}$$

The associated boundary conditions are

$$q_m(0,t) = 0, \quad \frac{\partial q_m(L,t)}{\partial x_0} = 0.$$

It follows that τ_k^m evolves according to

$$D_m \frac{\partial^2 \tau_k^m(x_0)}{\partial x_0^2} + \sum_{n=0,1} A_{mn}^\top \tau_n(x_0) = -I_{(a_k,a_{k+1})}(x), \tag{2.10}$$

supplemented by the boundary conditions

$$\tau_k^m(0) = 0, \quad \tau_k^{m\prime}(L) = 0.$$

2.2. Probabilistic formulation

One could determine the mean residence times τ_k^m by explicitly solving the piecewise differential equations (2.10). However, this becomes considerably more involved in the gated case, see section 3. Therefore, we will consider an alternative, probabilistic formulation of the above process, which will allow us to apply methods developed in previous work to the analysis of gated residence times [7]. In addition to simplifying the analysis, our approach has a number of other advantages. First, it provides insights into the nature of sample paths that contribute to the residence times. Second, the method can be extended to Brownian particles moving in a potential V, for which equation (2.2) becomes $\mathrm{d}X(t) = V(X)\mathrm{d}t + \sqrt{2D_n}\,\mathrm{d}W(t)$. Although the resulting Chapman–Kolmogorov equation cannot be solved exactly, except for special choices of V, qualitative aspects of the dynamics can be obtained using the probabilistic approach, see for example [4, 5].

For ease of notation we drop the subscript on the initial position x_0. Before proceeding, it is useful to recall a few basic definitions from probability theory.

Conditional expectations and the tower property. Consider a sample space Ω with σ-algebra $\mathcal{F}$ and probability measure $\mathbb{P}$. In the case of two random variables on the probability space $(\Omega, \mathcal{F}, \mathbb{P})$, we define the *conditional expectation* of Y given X by

$$\mathbb{E}(Y|X) = \int y\rho(y|X)\mathrm{d}y,$$

where $\rho(y|X)$ is the conditional probability density with respect to X. This definition can be generalized to conditional expectation with respect to a σ-algebra (instead of with respect to a random variable), see [13, 15]. The conditional expectation satisfies

$$\mathbb{E}(\mathbb{E}(Y|X)) \equiv \int\int y\rho(y|x)\rho(x)\mathrm{d}y\mathrm{d}x = \int y\rho_2(y,x)\mathrm{d}y\mathrm{d}x = \mathbb{E}(Y),$$

where ρ_2 is a joint probability density. Using a similar argument, one can also derive the *tower property*

$$\mathbb{E}(\mathbb{E}(Y|X_1, X_2)|X_1) = \mathbb{E}(Y|X_1).$$

Stopping times and the strong Markov property. Let $X = \{X(t), t \in \mathbb{R}^+\}$ be a continuous stochastic process defined on $(\Omega, \mathcal{F}, \mathbb{P})$. The σ-algebra generated by the stochastic process X up to time t then corresponds to sets of sample paths, realizations or trajectories $\{X(s), 0 \leqslant s \leqslant t\}$. A stopping time $\mathcal{T}$ is a time that depends on the path $\{X(t), t \in \mathbb{R}^+\}$, and is thus a random variable. A defining feature of a stopping time is that one knows at time t whether or not $\mathcal{T} \leqslant t$, that is, knowledge of the sample path $\{X(s), s \leqslant t\}$ is sufficient to determine whether or not $\mathcal{T} \leqslant t$. It immediately follows that the first passage time (2.5) is a stopping time. Given any stopping time $\mathcal{T}$ with respect to X, if the stochastic process $Y(t) = X(t + \mathcal{T}) - X(\mathcal{T})$ is independent of $\{X(s), s < \mathcal{T}\}$ then X is said to satisfy the strong Markov property.

We will make repeated use of the strong Markov property and conditional expectations in the following. Define the first time the particle reaches position $y \in [a_0, a_m]$ when the jump process is in state $n \in \{0, 1\}$,

$$s_y^n := \inf\big\{t > 0 : \{X(t) = y\} \cap \{n(t) = n\}\big\}. \tag{2.11}$$

For any stopping time S, we denote the σ-algebra generated by the process $\{(X(t), n(t))\}_{t=0}^{S}$ until time S by $\mathcal{F}(S)$. If $x \in [a_0, a_k]$, then by the tower property of conditional expectation and the strong Markov property, we have that

$$\begin{aligned}
\tau_k^n(x) &= \mathbb{E}_{x,n}[\mathcal{T}_k 1_{s_{a_k}^0 < \mathcal{T}} 1_{s_{a_k}^0 < s_{a_k}^1}] + \mathbb{E}_{x,n}[\mathcal{T}_k 1_{s_{a_k}^1 < \mathcal{T}} 1_{s_{a_k}^1 < s_{a_k}^0}] \\
&= \mathbb{E}_{x,n}[1_{s_{a_k}^0 < \mathcal{T}} 1_{s_{a_k}^0 < s_{a_k}^1} \mathbb{E}_{x,n}[\mathcal{T}_k | \mathcal{F}(s_{a_k}^0)]] \\
&\quad + \mathbb{E}_{x,n}[1_{s_{a_k}^1 < \mathcal{T}} 1_{s_{a_k}^1 < s_{a_k}^0} \mathbb{E}_{x,n}[\mathcal{T}_k | \mathcal{F}(s_{a_k}^1)]] \\
&= \mathbb{P}_{x,n}(\{s_{a_k}^0 < \mathcal{T}\} \cap \{s_{a_k}^0 < s_{a_k}^1\}) \tau_k^0(a_k) \\
&\quad + \mathbb{P}_{x,n}(\{s_{a_k}^1 < \mathcal{T}\} \cap \{s_{a_k}^1 < s_{a_k}^0\}) \tau_k^1(a_k).
\end{aligned} \tag{2.12}$$

Since we will be using similar arguments throughout the paper, it is worthwhile deconstructing this result. The first equality simply states that conditioning the residence time $\mathcal{T}_k$ on the particle entering the interval $[a_k, a_{k+1}]$ is trivial when $x < a_k$, since $\mathcal{T}_k = 0$ otherwise. The second equality is an application of the tower property, whereas the third uses the strong Markov property and the fact that there is no contribution to the residence time prior to first entering the interval $[a_k, a_{k+1}]$. Similarly, if $x \in [a_{k+1}, a_m]$, then

$$\begin{aligned}
\tau_k^n(x) &= \mathbb{E}_{x,n}[\mathcal{T}_k 1_{s_{a_{k+1}}^0 < s_{a_{k+1}}^1}] + \mathbb{E}_{x,n}[\mathcal{T}_k 1_{s_{a_{k+1}}^1 < s_{a_{k+1}}^0}] \\
&= \mathbb{P}_{x,n}(s_{a_{k+1}}^0 < s_{a_{k+1}}^1) \tau_k^0(a_{k+1}) \\
&\quad + \left(1 - \mathbb{P}_{x,n}(s_{a_{k+1}}^0 < s_{a_{k+1}}^1)\right) \tau_k^1(a_{k+1}).
\end{aligned} \tag{2.13}$$

In order to use (2.12) and (2.13) to calculate τ_k, we will obtain explicit expressions for the splitting probabilities

$$\begin{aligned}
p_k^n(x) &:= \mathbb{P}_{x,n}(\{s_{a_k}^0 < \mathcal{T}\} \cap \{s_{a_k}^0 < s_{a_k}^1\}), \quad x \in [0, a_k] \\
\widetilde{p}_k^n(x) &:= \mathbb{P}_{x,n}(\{s_{a_k}^1 < \mathcal{T}\} \cap \{s_{a_k}^1 < s_{a_k}^0\}), \quad x \in [0, a_k] \\
q_k^n(x) &:= \mathbb{P}_{x,n}(s_{a_{k+1}}^0 < s_{a_{k+1}}^1), \quad x \in [a_{k+1}, a_m].
\end{aligned}$$

We will find it convenient to work with the following sums and differences

$$S_\tau := \tau_k^0 + \tau_k^1, \quad \Delta_\tau := \tau_k^0 - \tau_k^1,$$

with S_p, Δ_p, $S_{\tilde{p}}$, $\Delta_{\tilde{p}}$, and S_q, Δ_q defined analogously. In these new variables, (2.12) and (2.13) become

$$S_\tau(x) = \begin{cases} \frac{1}{2}(S_p(x) + S_{\tilde{p}}(x)) S_\tau(a_k) + \frac{1}{2}(S_p(x) - S_{\tilde{p}}(x)) \Delta_\tau(a_k), & x \in [0, a_k] \\ S_\tau(a_{k+1}) + (S_q(x) - 1) \Delta_\tau(a_{k+1}), & x \in [a_{k+1}, a_m] \end{cases} \tag{2.14}$$

and

$$\Delta_\tau(x) = \begin{cases} \frac{1}{2}(\Delta_p(x) + \Delta_{\tilde{p}}(x)) S_\tau(a_k) + \frac{1}{2}(\Delta_p(x) - \Delta_{\tilde{p}}(x)) \Delta_\tau(a_k), & x \in [0, a_k] \\ \Delta_q(x) \Delta_\tau(a_{k+1}), & x \in [a_{k+1}, a_m] \end{cases} \tag{2.15}$$

Following our previous work [3, 4, 7] one can show that Δ_p and S_p satisfy the following ODEs on (a_0, a_k)

$$\mathcal{L}\Delta_p - \Gamma_+ \Delta_p = 0, \tag{2.16a}$$

$$\mathcal{L}S_p - \Gamma_-\Delta_p = 0,, \tag{2.16b}$$

where

$$\mathcal{L} := \frac{\mathrm{d}^2}{\mathrm{d}x^2}, \quad \Gamma_\pm := \frac{D_1\beta \pm D_0\alpha}{D_1 D_0}, \tag{2.17}$$

with boundary conditions

$$\Delta_p(a_0) = S_p(a_0) = 0, \quad \Delta_p(a_k) = S_p(a_k) = 1. \tag{2.18}$$

Further, $\Delta_{\tilde{p}}$ and $S_{\tilde{p}}$ satisfy (2.16*a*) and (2.16*b*) and (2.18), except the boundary condition for $\Delta_{\tilde{p}}$ at $x = a_k$ is $\Delta_{\tilde{p}}(a_k) = -1$. It follows that

$$\Delta_{\tilde{p}} = -\Delta_p, \tag{2.19}$$

and thus

$$\mathcal{L}(S_p + S_{\tilde{p}}) = 0 \tag{2.20a}$$

$$\mathcal{L}(S_p - S_{\tilde{p}}) - 2\Gamma_-\Delta_p = 0, \tag{2.20b}$$

with boundary conditions

$$(S_p + S_{\tilde{p}})(a_0) = 0, \quad (S_p + S_{\tilde{p}})(a_k) = 2$$
$$(S_p - S_{\tilde{p}})(a_0) = 0, \quad (S_p - S_{\tilde{p}})(a_k) = 0.$$

Similarly, Δ_q and S_q satisfy (2.16*a*) and (2.16*b*) on (a_{k+1}, a_m) with boundary conditions

$$\Delta_q(a_{k+1}) = S_q(a_{k+1}) = 1$$
$$\Delta_q'(a_m) = S_q'(a_m) = 0.$$

We can now solve these boundary value problems explicitly and obtain exact expressions for Δ_p, $S_p + S_{\tilde{p}}$, $S_p - S_{\tilde{p}}$, Δ_q, and S_q. Setting $a_j = jl$ for each $j \in \{0, 1, \ldots, m\}$, we have

$$\begin{aligned}
\Delta_p(x) &= \mathrm{csch}(\sqrt{\Gamma_+}kl)\sinh(\sqrt{\Gamma_+}x), \\
(S_p + S_{\tilde{p}})(x) &= 2x/(kl), \\
(S_p - S_{\tilde{p}})(x) &= \frac{2\Gamma_-\left[kl\sinh(\sqrt{\Gamma_+}x)\mathrm{csch}(\sqrt{\Gamma_+}kl) - x\right]}{\Gamma_+ kl}, \\
\Delta_q(x) &= \mathrm{sech}\big(\sqrt{\Gamma_+}(m-(k+1))l\big)\cosh\left(\sqrt{\Gamma_+}(ml - x)\right), \\
S_q(x) &= \frac{\Gamma_-}{\Gamma_+}(\Delta_q(x) - 1) + 1.
\end{aligned}$$

It remains to determine Δ_τ and S_τ on $[a_k, a_{k+1}]$. Again, following our previous work [3, 4, 7] one can show that Δ_τ and S_τ satisfy the following ODEs on (a_k, a_{k+1})

$$\mathcal{L}\Delta_\tau - \Gamma_+\Delta_\tau = -\gamma_- \tag{2.21a}$$

$$\mathcal{L}S_\tau - \Gamma_-\Delta_\tau = -\gamma_+, \tag{2.21b}$$

where

$$\gamma_\pm := \frac{D_1 \pm D_0}{D_1 D_0}.$$

Differentiating (2.14) and (2.15) and imposing continuity yields the boundary conditions

$$S'_\tau(a_k) = \frac{1}{2}(S'_p(a_k) + S'_{\tilde{p}}(a_k))S_\tau(a_k) + \frac{1}{2}(S'_p(a_k) - S'_{\tilde{p}}(a_k))\Delta_\tau(a_k)$$
$$\Delta'_\tau(a_k) = \Delta'_p(a_k)\Delta_\tau(a_k) \tag{2.22}$$

$$S'_\tau(a_{k+1}) = S'_q(a_{k+1})\Delta_\tau(a_{k+1})$$
$$\Delta'_\tau(a_{k+1}) = \Delta'_q(a_{k+1})\Delta_\tau(a_{k+1}). \tag{2.23}$$

We have used (2.19) in (2.22) and (2.23). Again we can solve this boundary value problem explicitly and obtain explicit expressions for S_τ and Δ_τ. In particular, with $a_j = jl$ for each $j \in \{0, 1, \ldots, m\}$, we have that

$$\begin{aligned}
\Delta_\tau(x) = \frac{\gamma_-}{\Gamma_+} - \frac{\gamma_-}{2\Gamma_+}\operatorname{sech}\big(\sqrt{\Gamma_+}ml\big)\Big[&\cosh\big(\sqrt{\Gamma_+}((k+1-m)l - x)\big)\\
&+ \cosh\big(\sqrt{\Gamma_+}((k+m)l - x)\big) + \cosh\big(\sqrt{\Gamma_+}((k-m)l + x)\big)\\
&- \cosh\big(\sqrt{\Gamma_+}((k+1-m)l + x)\big)\Big],
\end{aligned}$$

$$\begin{aligned}
S_\tau(x) = \frac{\mathrm{e}^{-\sqrt{\Gamma_+}(2kl+l+x)}}{4\Gamma_+^2}\Big[&2\mathrm{e}^{\sqrt{\Gamma_+}(2kl+l+x)}\Big(\gamma_-\Gamma_-\big(\Gamma_+\big(k^2l^2 - 2(k+1)lx + x^2\big) + 2\big)\\
&- \gamma_+\Gamma_+^2\big(k^2l^2 - 2(k+1)lx + x^2\big)\Big)\\
&+ \gamma_-\Gamma_-(\mathrm{e}^{\sqrt{\Gamma_+}l} - 1)\mathrm{e}^{\sqrt{\Gamma_+}kl}\Big((\mathrm{e}^{\sqrt{\Gamma_+}(2kl+l)} + \mathrm{e}^{2\sqrt{\Gamma_+}x} - 1)\tanh(\sqrt{\Gamma_+}ml)\\
&+ \operatorname{sech}(\sqrt{\Gamma_+}ml)\mathrm{e}^{\sqrt{\Gamma_+}(2kl-lm+l+2x)} - 1\Big)\\
&- \gamma_-\Gamma_-\big(\mathrm{e}^{\sqrt{\Gamma_+}(kl+2x)} + \mathrm{e}^{\sqrt{\Gamma_+}(kl+l+2x)} + \mathrm{e}^{\sqrt{\Gamma_+}(3kl+l)} + \mathrm{e}^{\sqrt{\Gamma_+}(3k+2)l}\big)\Big].
\end{aligned}$$

2.3. Results

In applications, one is not typically interested in the initial discrete state $n(0)$. Therefore, in the following we will assume that $n(t)$ starts in its invariant measure,

$$\mathbb{P}(n(t) = 0) = \rho_0 := \frac{\alpha}{\alpha + \beta}, \quad \mathbb{P}(n(t) = 1) = \rho_1 := \frac{\beta}{\alpha + \beta}.$$

and set $\tau_k = \rho_0\tau_k^0 + \rho_1\tau_k^1$. Thus all of our numerical results will be in terms of τ_k rather than the components τ_k^m. We fix the units of length by setting $l = 1$ and taking a baseline switching rate to be $\alpha = \beta = 1$. Within the context of cell biology we would typically have $l = 1$ μm and $\alpha = 1$ s^{-1} so that D varies between 0.01–10 μm^2 s^{-1}.

Plotting the various explicit formulae reveals that diffusion with temporal disorder exhibits some qualitative behavior not seen in diffusion with spatial disorder [9, 23, 24]. In particular, figure 3 shows that $\tau_k(x)$ (the expected residence time in $[a_k, a_{k+1}]$ before absorption at a_0 given initial position x) is not monotonically increasing in x. For diffusion without temporal disorder, $\tau_k(x)$ is monotonically increasing in x because starting further away from a_0 increases the first passage time to a_0 and therefore can only increase the time spent in $[a_k, a_{k+1}]$. However, this line of reasoning is violated if the diffusion coefficient changes in time. To see this, suppose $D_1 \gg 1$ so that the particle is absorbed at a_0 almost immediately once the diffusion coefficient becomes D_1. Hence, the only appreciable residence time in $[a_k, a_{k+1}]$ is accumulated when

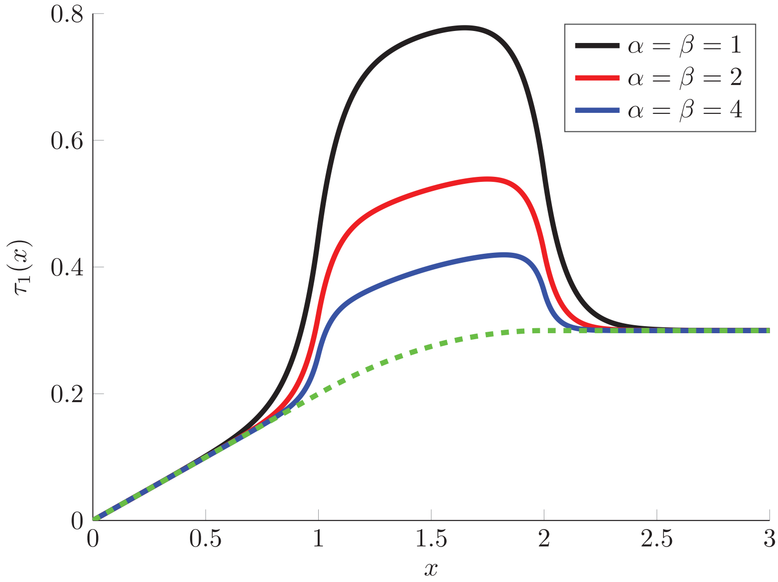

Figure 3. Expected residence time is non-monotonic in starting position. Here, $D_0 = 0.01$, $D_1 = 10$, $a_0 = 0$, $l = 1$, and $a_m = 3$. The monotonically increasing green dashed curve is with $D_0 = D_1 = \frac{1}{2}(0.01) + \frac{1}{2}(10)$ and thus with no temporal heterogeneity. (Smaller amplitude solid curves correspond to faster switching rates.)

the diffusion coefficient is D_0. Further, suppose that $D_0 \ll 1$ so that the particle is unlikely to move very far from its initial position before the diffusion coefficient becomes D_1. Thus, if the initial condition is outside of $[a_k, a_{k+1}]$ (or inside $[a_k, a_{k+1}]$ but near a_k or a_{k+1}), then $\tau_k(x)$ will be much less than if x was closer to the center of $[a_k, a_{k+1}]$.

In addition, figure 4 shows that increasing the diffusion coefficient can actually increase the expected residence time. To see how temporal disorder can yield this counterintuitive result, suppose that $D_0 \ll 1$, $D_1 \gg 1$, and $x \notin [a_k, a_{k+1}]$. Thus, the particle will not accumulate much residence time in $[a_k, a_{k+1}]$ before absorption at a_0 because it is unlikely to enter $[a_k, a_{k+1}]$ when the diffusion coefficient is D_0 (because $x \notin [a_k, a_{k+1}]$ and $D_0 \ll 1$), and the particle will be absorbed almost immediately once the diffusion coefficient becomes D_1 (because $D_1 \gg 1$). However, increasing D_0 increases the probability that the particle will enter $[a_k, a_{k+1}]$ and thereby increases the expected residence time in $[a_k, a_{k+1}]$ before absorption at a_0.

We now investigate how $\tau_k(x)$ depends on the switching rate $\alpha + \beta$. In the slow switching limit ($\alpha + \beta \ll 1$), the diffusion coefficient is very unlikely to switch before the particle is absorbed, so the expected residence time is simply the average

$$\tau_k(x) \approx \rho_0 T(x; D_0) + \rho_1 T(x; D_1), \tag{2.24}$$

where $T(x;D)$ is the expected residence time given that the diffusion coefficient is always D, which is of course a classical object. On the other hand, in the fast switching limit ($\alpha + \beta \gg 1$), switching between diffusion coefficients D_0 and D_1 averages to an effective diffusion coefficient $\rho_0 D_0 + \rho_1 D_1$ (see [8]) so that the expected residence time becomes

$$\tau_k(x) \approx T(x; \rho_0 D_0 + \rho_1 D_1). \tag{2.25}$$

Figure 5 shows that $\tau_k(x)$ decreases from (2.24) to (2.25) as the switching rate $\alpha + \beta$ increases.

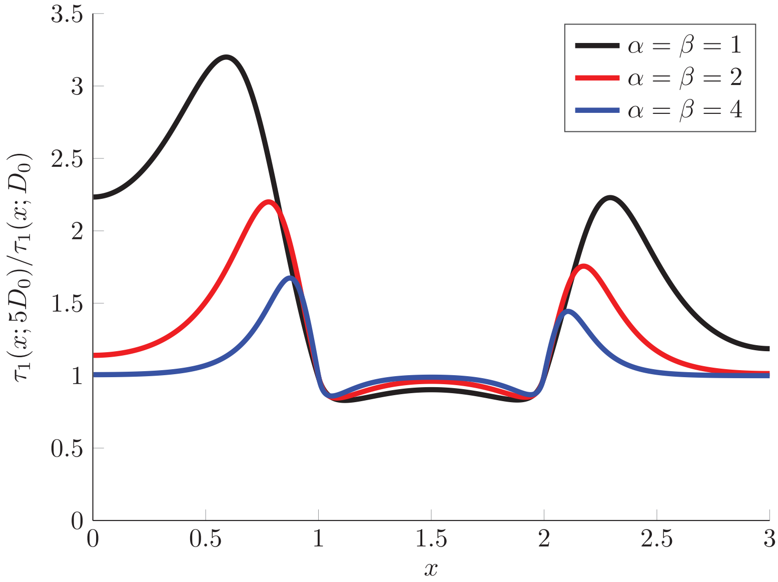

Figure 4. Increasing the diffusion coefficient can increase the expected residence time. The ratio of $\tau_1(x; 5D_0)$ to $\tau_1(x; D_0)$ is plotted as a function of initial condition x. $\tau_1(x, D_0)$ is the expected residence time in $[a_1, a_2]$ with diffusion coefficient $D_0 = 0.01$ when $n(t) = 0$ and diffusion coefficient $D_1 = 100$ when $n(t) = 1$. $\tau_1(x, 5D_0)$ is the same expected residence time except the diffusion coefficient is 5 times larger when $n(t) = 0$. Notably, this ratio is greater than one for most initial conditions. Here, $a_0 = 0$, $l = 1$, and $a_m = 3$. (Smaller amplitude solid curves correspond to faster switching rates.)

2.4. Higher spatial dimensions

The above analysis of residence times can be extended to higher spatial dimensions. Following [24], consider a Brownian particle diffusing in a spherically symmetric domain with an absorbing inner boundary at radius a_0 and a reflecting outer boundary at radius a_m. Thus, the radial position of the particle $X(t) \in [a_0, a_m]$ evolves according to the SDE

$$\mathrm{d}X(t) = D_n \frac{\mathrm{d}-1}{X(t)}\,\mathrm{d}t + \sqrt{2D_n}\,\mathrm{d}W(t), \tag{2.26}$$

when $n(t) = n \in \{0, 1\}$. As in section 2.2, we would like to compute the expected value of $\mathcal{T}_k$ as a function of starting position with $\mathcal{T}_k$ the residence time in the interval $[a_k, a_{k+1}]$. The analysis is almost identical except that the differential operator $\mathcal{L}$ of equation (2.17) becomes

$$\mathcal{L} := \frac{\mathrm{d}-1}{x}\frac{\mathrm{d}}{\mathrm{d}x} + \frac{\mathrm{d}^2}{\mathrm{d}x^2}, \qquad \Gamma_\pm := \frac{D_1\beta \pm D_0\alpha}{D_1 D_0}, \tag{2.27}$$

The resulting analytical expressions are considerably more complicated, and require the use of a symbolic package such as Mathematica. For the sake of illustration, the relevant expressions in the two-dimensional case are given in the appendix.

In figure 6 we illustrate how the expected residence time in the kth interval, $[a_k, a_{k+1}]$, grows as a function of k for different spatial dimensions, $d \in \{1, 2, 3\}$. We find that this expected residence time grows like k^{d-1}, which is the size of the d-dimensional annular region defined by a radius between a_k and a_{k+1}. That is, let $S_k(d)$ denote the size of this kth region in dimension d. Hence,

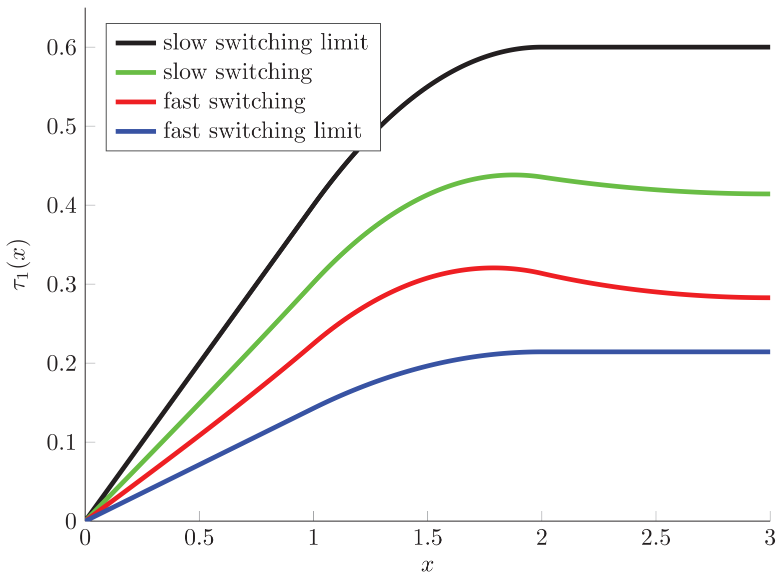

Figure 5. Expected residence time $\tau_k(x)$ as a function of initial condition, x, for various switching rates, $\alpha + \beta$. Here, $D_0 = 1$, $D_1 = 10$, $a_0 = 0$, $l = 1$, and $a_m = 3$. The green curve has $\alpha = 0.1$, $\beta = 0.2$. The red curve has $\alpha = 0.4$, $\beta = 0.8$. The black curve is (2.24) and the blue curve is (2.25). (Smaller amplitude solid curves correspond to faster switching rates.)

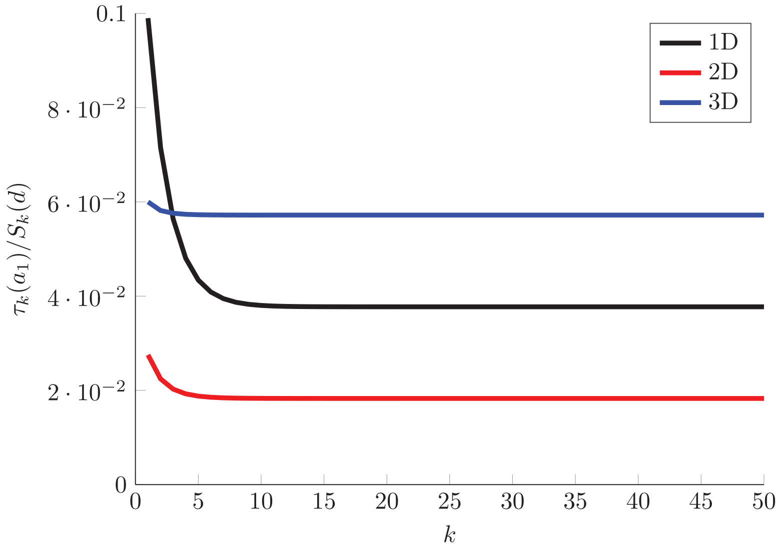

Figure 6. Expected residence time in the kth interval grows like k^{d-1} in spatial dimension d. The ratio $\tau_k(a_1)/S_k(d)$ is plotted as a function of k, where $S_k(d)$ is the size of the d-dimensional annular region defined by a radius between a_k and a_{k+1}, defined in (2.28*a*)–(2.28*c*). Here, $D_0 = 3$, $D_1 = 50$, $\alpha = 1$, $\beta = 1$, $a_0 = 0.05$, $l = 1$, and $a_m = 100$. (Top curve is 3D, middle curve is 1D, and bottom curve is 2D.)

$$S_k(1) = (k+1)l - kl = l \tag{2.28a}$$

$$S_k(2) = \pi(a_0 + (k+1)l)^2 - \pi(a_0 + kl)^2 \approx k \tag{2.28b}$$

$$S_k(3) = \frac{4}{3}\pi(a_0 + (k+1)l)^3 - \frac{4}{3}\pi(a_0 + kl)^3 \approx k^2. \tag{2.28c}$$

Figure 6 shows that the ratio $\tau_k(a_1)/S_k(d)$ is constant for large k.

3. Gated residence times

Now, suppose that each internal boundary at $x = a_k$ is stochastically-gated. That is, there is a Markov jump process $n(t) \in \{0, 1\}$,

$$0 \underset{\alpha}{\overset{\beta}{\rightleftharpoons}} 1,$$

so that the particle cannot pass through $x = a_k$ if $n(t) = 1$ (see figure 1(b)). Moreover, we take the diffusion coefficient to depend on the conformational state, $n(t)$, as in section 2. Of course, if we want to consider the effects of the gating only (and not the switching diffusion coefficient), we can take $D_0 = D_1$. For the sake of simplicity, we focus on the 1D problem.

Following section 2, we would like to compute the expected value of $\mathcal{T}_k$ as a function of starting position, so we again decompose $\tau_k = \rho_0\tau_k^0 + \rho_1\tau_k^1$ with

$$\tau_k^n(x) = \mathbb{E}_{x,n}[\mathcal{T}_k].$$

Define the splitting probability r_k^n by

$$r_k^n(x) = \mathbb{P}_{x,n}(s_{a_k}^0 < \mathcal{T}),$$

where $s_{a_k}^0$ is as in (2.11). If $x \in [0, a_k)$, then by the tower property of conditional expectation and the strong Markov property, we have that

$$\begin{aligned}\tau_k^n(x) = \mathbb{E}_{x,n}[\mathcal{T}_k 1_{s_{a_k}^0 < \mathcal{T}}] &= \mathbb{E}_{x,n}[1_{s_{a_k}^0 < \mathcal{T}} \mathbb{E}_{x,n}[\mathcal{T}_k | \mathcal{F}(s_{a_k}^0)]] \\ &= \mathbb{P}_{x,n}(s_{a_k}^0 < \mathcal{T})\mathbb{E}_{a_k,0}[\mathcal{T}_k] \\ &= r_k^n(x)\tau_k^0(a_k).\end{aligned} \tag{3.1}$$

Further, if $x > a_{k+1}$ then

$$\begin{aligned}\tau_k^n(x) = \mathbb{E}_{x,n}[\mathbb{E}_{x,n}[\mathcal{T}_k | \mathcal{F}(s_{a_{k+1}}^0)]] &= \mathbb{E}_{a_{k+1},0}[\mathcal{T}_k] \\ &= \tau_k^0(a_{k+1}).\end{aligned} \tag{3.2}$$

Thus, we now need to determine the splitting probability $r_k^0(x)$ in order to determine $\tau_k(x)$. We will do this three steps.

First, we show that if $x \in (a_j, a_{j+1})$, then $r_k^n(x)$ is an average of $r_k^0(a_j)$ and $r_k^0(a_{j+1})$. By the strong Markov property,

$$\begin{aligned}r_k^n(x) &= \mathbb{P}_{x,n}(s_{a_k}^0 < \mathcal{T} \mid s_{a_j}^0 < s_{a_{j+1}}^0)\mathbb{P}_{x,n}(s_{a_j}^0 < s_{a_{j+1}}^0) \\ &\quad + \mathbb{P}_{x,n}(s_{a_k}^0 < \mathcal{T} \mid s_{a_j}^0 > s_{a_{j+1}}^0)\mathbb{P}_{x,n}(s_{a_j}^0 > s_{a_{j+1}}^0) \\ &= \mathbb{P}_{a_j,0}(s_{a_k}^0 < \mathcal{T})\mathbb{P}_{x,n}(s_{a_j}^0 < s_{a_{j+1}}^0) \\ &\quad + \mathbb{P}_{a_{j+1},0}(s_{a_k}^0 < \mathcal{T})\mathbb{P}_{x,n}(s_{a_j}^0 > s_{a_{j+1}}^0) \\ &= r_k^0(a_j)[1 - \overline{p}_j^n(x)] + r_k^0(a_{j+1})\overline{p}_j^n(x),\end{aligned}$$

where $\overline{p}_j^n(x) := \mathbb{P}_{x,n}(s^0_{a_j} > s^0_{a_{j+1}})$. Following our previous work [3, 4, 7] one can show that $\overline{p}_j^n$ satisfies the following ODEs on (a_j, a_{j+1})

$$D_0\mathcal{L}\overline{p}_j^0 + \beta(\overline{p}_j^1 - \overline{p}_j^0) = 0, \tag{3.3a}$$

$$D_1\mathcal{L}\overline{p}_j^1 + \alpha(\overline{p}_j^0 - \overline{p}_j^1) = 0, \tag{3.3b}$$

where $\mathcal{L}$ is the differential operator defined in (2.17), with boundary conditions

$$\overline{p}_j^0(a_j) = \frac{\mathrm{d}}{\mathrm{d}x}\overline{p}_j^1(a_j) = \frac{\mathrm{d}}{\mathrm{d}x}\overline{p}_j^1(a_{j+1}) = 0, \quad \text{and} \quad \overline{p}_j^0(a_{j+1}) = 1.$$

One can solve this boundary value problem explicitly and obtain explicit expressions for $\overline{p}_j^n$. In dimension $d = 1$:

$$\begin{aligned}\overline{p}_j^0(x) = &\frac{\beta D_1^{3/2}\left(\sinh\left((-jl + l/2 + x)\Lambda\right) + \sinh\left(\frac{l}{2}\Lambda\right)\right)}{2\beta D_1^{3/2}\sinh\left(\frac{l}{2}\Lambda\right) + \alpha l\sqrt{D_0(\alpha D_0 + \beta D_1)}\cosh\left(\frac{l}{2}\Lambda\right)} \\ &+ \frac{\alpha(-jl + l + x)\sqrt{D_0(\alpha D_0 + \beta D_1)}\cosh\left(\frac{l}{2}\Lambda\right)}{2\beta D_1^{3/2}\sinh\left(\frac{l}{2}\Lambda\right) + \alpha l\sqrt{D_0(\alpha D_0 + \beta D_1)}\cosh\left(\frac{l}{2}\Lambda\right)},\end{aligned} \tag{3.4}$$

$$\begin{aligned}\overline{p}_j^1(x) = &\frac{\sqrt{D_1}\left(\beta D_1\sinh\left(\frac{l}{2}\Lambda\right) - \alpha D_0\sinh\left((-jl + l/2 + x)\Lambda\right)\right)}{2\beta D_1^{3/2}\sinh\left(\frac{l}{2}\Lambda\right) + \alpha l\sqrt{D_0(\alpha D_0 + \beta D_1)}\cosh\left(\frac{l}{2}\Lambda\right)} \\ &+ \frac{\alpha(-jl + l + x)\sqrt{D_0(\alpha D_0 + \beta D_1)}\cosh\left(\frac{l}{2}\Lambda\right)}{2\beta D_1^{3/2}\sinh\left(\frac{l}{2}\Lambda\right) + \alpha l\sqrt{D_0(\alpha D_0 + \beta D_1)}\cosh\left(\frac{l}{2}\Lambda\right)},\end{aligned} \tag{3.5}$$

where

$$\Lambda = \sqrt{\frac{\alpha}{D_1} + \frac{\beta}{D_0}}. \tag{3.6}$$

Finally, to determine r_k^0 it remains to find the $k-1$ constants, $\{r_k^0(a_j)\}_{j=1}^{k-1}$. Similar to the argument above, one can show that if $1 \leqslant j \leqslant k$, then $r_k^0(a_j)$ is an average of its neighbors, $r_k^0(a_{j-1})$ and $r_k^0(a_{j+1})$,

$$r_k^0(a_j) = (1 - Q_j)r_x^0(a_{j-1}) + Q_j r_x^0(a_{j+1}), \tag{3.7}$$

where Q_j is found by solving a certain boundary value problem. In particular, $Q_j = \overline{q}_j^0(a_j)$ where $\overline{q}_j^n(x)$ satisfies

$$\begin{aligned}&D_0\mathcal{L}\overline{q}_j^0 + \beta(\overline{q}_j^1 - \overline{q}_j^0) = 0, \quad x \in (a_{j-1}, a_j) \cup (a_j, a_{j+1}), \\ &D_1\mathcal{L}\overline{q}_j^1 + \alpha(\overline{q}_j^0 - \overline{q}_j^1) = 0, \quad x \in (a_{j-1}, a_j) \cup (a_j, a_{j+1}),\end{aligned}$$

with boundary conditions

$$\overline{q}_j^0(a_{j-1}) = \frac{\mathrm{d}}{\mathrm{d}x}\overline{q}_j^1(a_{j-1}) = \frac{\mathrm{d}}{\mathrm{d}x}\overline{q}_j^1(a_j) = \frac{\mathrm{d}}{\mathrm{d}x}\overline{q}_j^1(a_j) = \frac{\mathrm{d}}{\mathrm{d}x}\overline{q}_j^1(a_{j+1}) = 0, \quad \overline{q}_j^0(a_{j+1}) = 1,$$

and continuity conditions

$$\overline{q}_j^0(0-) = \overline{q}_j^0(0+), \quad \text{and} \quad \frac{\mathrm{d}}{\mathrm{d}x-}\overline{q}_j^0(a_j) = \frac{\mathrm{d}}{\mathrm{d}x+}\overline{q}_j^0(a_j).$$

In the case of uniform spacing, $a_k = kl$, and one space dimension $d = 1$, symmetry ensures that $Q_j = 1/2$. Thus in this case, rearranging (3.7) yields that the constants $\{r_k^0(a_j)\}_{j=1}^k$ satisfy a discretized Laplace equation

$$r_k^0(a_{j-1}) - 2r_k^0(a_j) + r_k^0(a_{j+1}) = 0,$$

with boundary conditions $r_k^0(a_0) = 0$ and $r_k^0(a_k) = 1$. Thus,

$$r_k^0(a_j) = \frac{j}{k}.$$

Putting this together, we have that

$$\frac{\mathrm{d}}{\mathrm{d}x} r_k^0(a_k) = \frac{1}{k}\frac{\mathrm{d}}{\mathrm{d}x}\overline{p}_k^0(a_k).$$

Now, with this explicit value of r_k^n, we can find an explicit formula for $\tau_k = \rho_0\tau_k^0 + \rho_1\tau_k^1$. In particular, following our previous work [3, 4, 7] one can show that τ_k^n satisfies the following ODEs on (a_k, a_{k+1})

$$D_0\mathcal{L}\tau_k^0 + \beta(\tau_k^1 - \tau_k^0) = -1 \tag{3.8a}$$

$$D_1\mathcal{L}\tau_k^1 + \alpha(\tau_k^0 - \tau_k^1) = -1. \tag{3.8b}$$

Differentiating (3.1) and (3.2) and imposing continuity yields the boundary conditions

$$\frac{\mathrm{d}}{\mathrm{d}x}\tau_k^0(a_k) = \tau_k^0(a_k)\frac{\mathrm{d}}{\mathrm{d}x}r_k^0(a_k) = \tau_k^0(a_k)\frac{1}{k}\frac{\mathrm{d}}{\mathrm{d}x}\overline{p}_k^0(a_k), \tag{3.8c}$$

$$\frac{\mathrm{d}}{\mathrm{d}x}\tau_k^1(a_k) = 0, \tag{3.8d}$$

$$\frac{\mathrm{d}}{\mathrm{d}x}\tau_k^n(a_{k+1}) = 0. \tag{3.8e}$$

We have used that $\frac{\mathrm{d}}{\mathrm{d}x} r_k^1(a_k) = 0$ to obtain the no flux boundary conditions for τ_k^1. Solving this boundary value problem explicitly, we find that the expected residence time in the kth interval, $\tau_k(x) = \rho_0\tau_k^0(x) + \rho_1\tau_k^1(x)$, is

$$\begin{aligned}
\tau_k(x) = {} & \frac{1}{2A\alpha D_0(\alpha+\beta)(\alpha D_0+\beta D_1)^2}\Big[2A\beta l(\alpha+\beta)\sqrt{D_0D_1(\alpha D_0+\beta D_1)} \\
& \Big(\alpha(D_0-D_1)\mathrm{csch}(l\Lambda)\cosh\Big(\big[(k+1)l-x\big]\Lambda\Big) \\
& + D_1(\alpha+\beta)\coth(l\Lambda)\Big) - (\alpha D_0+\beta D_1) \\
& \Big(A\alpha D_0\Big(\alpha^2(kl-x)((k+2)l-x) + 2\beta(\alpha(kl-x)((k+2)l-x) - D_0 + D_1) \\
& + \beta^2(kl-x)((k+2)l-x)\Big) - 2l(\alpha+\beta)^2(\alpha D_0+\beta D_1)\Big)\Big],
\end{aligned}$$

where $A = \frac{1}{k}\frac{\mathrm{d}}{\mathrm{d}x}\overline{p}_k^0(a_k)$ and $\overline{p}_k^0$ is in (3.4).

In figure 7, we investigate how the expected residence time $\tau_k(x)$ depends on the switching rate $\alpha+\beta$. As in section 2, we find that the expected residence time decreases as the switching rate increases. We further find that the gates have no effect on the particle in the fast switching limit. We have observed this phenomenon in other works [3, 4, 7], and there are multiple ways

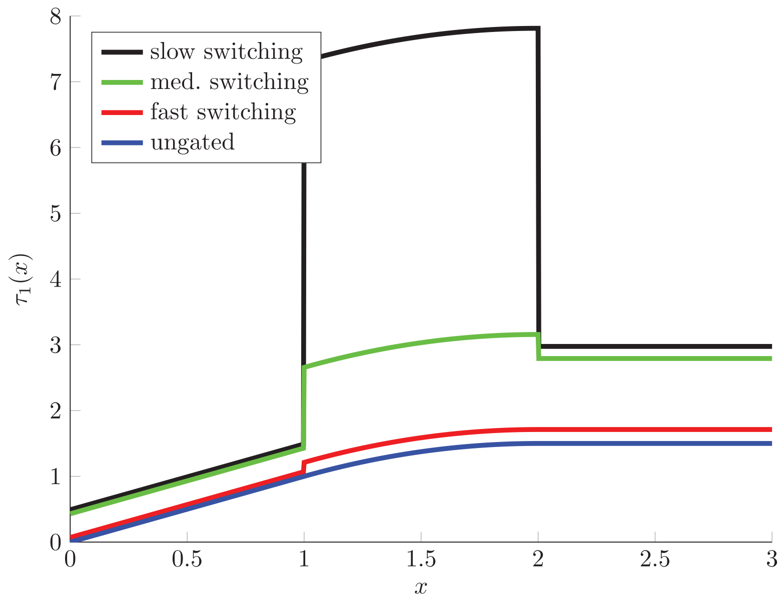

Figure 7. Gated expected residence time $\tau_k(x)$ as a function of initial condition, x, for various switching rates, $\alpha + \beta$. We see that the gates have no effect on the particle in the fast switching limit. Here, $D_0 = D_1 = 10$, $a_0 = 0$, $l = 1$, $a_m = 3$, and the spatial dimension is $d = 1$. The black curve has $\alpha = \beta = 0.1$, the green curve has $\alpha = \beta = 1$, the red curve has $\alpha = \beta = 100$. (Smaller amplitude solid curves correspond to faster switching rates.)

to understand it. The simplest explanation follows from the behavior of Brownian motion at fine spatial scales; namely, any time a Brownian particle hits a boundary, it hits it infinitely often. Thus, even if $n(t) = 1$ when the particle hits $x = a_k$, the particle will hit $x = a_k$ many times shortly after the first hit, and $n(t)$ must be equal to zero at one of those times if it is switching at a sufficiently high frequency. Indeed, if a Brownian particle starts on a boundary that switches between reflecting and absorbing, then the expected absorption time vanishes as the switching rate increases [4, 5].

4. Discussion

In this paper, we considered diffusion in a spherically symmetric d-dimensional domain and assumed that the particle randomly switches conformational state according to a Markov jump process. Motivated by various scenarios in cell biology, we supposed that (a) the diffusion coefficient depended on the conformational state and/or (b) the particle can only pass through a series of gates in the domain when it is in a particular conformational state. We calculated the expected residence time in certain portions of the domain before absorption at a boundary.

Our work can be viewed as a temporal analog of the work on diffusion in spatially heterogeneous media [9, 23, 24]. That is, while these previous studies supposed that the properties of the diffusing molecule change in space, we allowed the properties to change in time. In order to study this case of temporal heterogeneity, we developed probabilistic methods to analyze the problem. We found several new phenomena not seen in diffusion with only spatial heterogeneity, some of which are counterintuitive.

There are a number of possible extensions of our work. One is is to allow the rate at which the conformational state switches to depend on the position of the particle, thus resulting in a certain mix of spatial and temporal heterogeneity. This extension is natural because in cell biology, the change in conformational state of a molecule is often governed by binding or unbinding to a different molecule whose concentration varies across the cell. Another extension would be to consider a diffusion coefficient that depends on space (as in [24]) in the presence of stochastic gates. We expect that this analysis will depend crucially on whether one chooses the Ito, Stratonovich, or kinetic interpretations of the stochastic integral.

Acknowledgments

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Appendix

In this appendix, we collect some explicit formulas from section 2 for the two-dimensional case. Let I_n and K_n denote modified Bessel functions of the first and second kinds, respectively, and introduce the set of functions

$$f_{mn}(x,y) = I_n(\sqrt{\Gamma_+}x)K_n(\sqrt{\Gamma_+}y).$$

We then have the following expressions for the various functions used to determine the residence time in (a_k, a_{k+1}):

$$\begin{aligned}
\Delta_p(x) &= \frac{f_{00}(x,a_0) - f_{00}(a_0,x)}{f_{00}(a_k,a_0) - f_{00}(a_0,a_k)} \\
(S_p + S_{\bar{p}})(x) &= \frac{2\log\left(\frac{a_0}{x}\right)}{\log\left(\frac{a_0}{a_k}\right)} \\
(S_p - S_{\bar{p}})(x) &= -\frac{2\Gamma_-\left(\log\left(\frac{x}{a_0}\right)f_{00}(a_0,a_k) + \log\left(\frac{a_0}{a_k}\right)f_{00}(a_0,x) + \log\left(\frac{a_k}{a_0}\right)f_{00}(x,a_0) + \log\left(\frac{a_0}{x}\right)f_{00}(a_k,a_0)\right)}{\Gamma_+\log\left(\frac{a_0}{a_k}\right)\left(f_{00}(a_k,a_0) - f_{00}(a_0,a_k)\right)} \\
\Delta_q(x) &= \frac{f_{10}(a_m,x) + f_{01}(x,a_m)}{f_{10}(a_m,a_{k+1}) + f_{01}(a_{k+1},a_m)} \\
S_q(x) &= \frac{(\Gamma_+ - \Gamma_-)[f_{10}(a_m,a_{k+1}) + f_{01}(a_{k+1},a_m)] + \Gamma_-[f_{10}(a_m,x) + f_{01}(x,a_m)]}{\Gamma_+[f_{10}(a_m,a_{k+1}) + f_{01}(a_{k+1},a_m)]} \\
\Delta_\tau(x) &= \frac{\sqrt{\Gamma_+}\left[F_k(x) + \widetilde{F}_k(x) - G_k(x) - \widetilde{G}_k(x)\right] + \gamma_-[f_{10}(a_m,a_0) + f_{01}(a_0,a_m)]}{\Gamma_+[f_{10}(a_m,a_0) + f_{01}(a_0,a_m)]},
\end{aligned}$$

where

$$\begin{aligned}
F_k(x) &= \gamma_- f_{10}(a_m,x)[a_{k+1}f_{01}(a_0,a_{k+1}) - a_k f_{01}(a_0,a_k)] \\
\widetilde{F}_k(x) &= \gamma_- f_{01}(x,a_m)[a_{k+1}f_{10}(a_{k+1},a_0) - a_k f_{10}(a_k,a_0)] \\
G_k(x) &= \gamma_- f_{10}(a_m,a_0)\left[a_k f_{10}(a_k,x) + a_{k+1}f_{01}(x,a_{k+1})\right] \\
\widetilde{G}_k(x) &= \gamma_- f_{01}(a_0,a_m)\left[a_k f_{01}(x,a_k) + a_{k+1}f_{10}(a_{k+1},x)\right].
\end{aligned}$$

and

$$S_\tau(x) = \Big([f_{01}(a_0, a_m) + f_{10}(a_m, a_0)][H_k(x) + 4a_k\gamma_-\Gamma_-(f_{10}(a_k, a_k) + f_{01}(a_k, a_k))] + 4\Gamma_- \left[F_k(x) + \widetilde{F}_k(x) - G_k(x) - \widetilde{G}_k(x)\right] \Big) \Big(4\Gamma_+^{3/2}(f_{10}(a_m, a_0) + f_{01}(a_0, a_m))\Big)^{-1},$$

where

$$H_k(x) = \Big(-2a_k^2\gamma_-\Gamma_-\sqrt{\Gamma_+}\log\left(\frac{a_0}{a_k}\right) + 2a_k^2\gamma_+\Gamma_+^{3/2}\log\left(\frac{a_0}{a_k}\right) + 2a_{k+1}^2\gamma_-\Gamma_-\sqrt{\Gamma_+}\log\left(\frac{a_0}{a_k}\right) - 2a_{k+1}^2\gamma_+\Gamma_+^{3/2}\log\left(\frac{a_0}{a_k}\right) - a_k^2\gamma_-\Gamma_-\sqrt{\Gamma_+} + a_k^2\gamma_+\Gamma_+^{3/2} + 2a_{k+1}^2\gamma_-\Gamma_-\sqrt{\Gamma_+}\log(a_k) - 2a_{k+1}^2\gamma_+\Gamma_+^{3/2}\log(a_k) - 2a_{k+1}^2\gamma_-\Gamma_-\sqrt{\Gamma_+}\log(x) + 2a_{k+1}^2\gamma_+\Gamma_+^{3/2}\log(x) + \gamma_-\Gamma_-\sqrt{\Gamma_+}x^2 - \gamma_+\Gamma_+^{3/2}x^2 \Big).$$

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