Residence times of a Brownian particle with temporal heterogeneity

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Residence times of a Brownian particle with temporal heterogeneity

Paul C Bressloff and Sean D Lawley

Department of Mathematics, University of Utah, 155 South 1400 East, Salt Lake City, UT 84112, United States of America

E-mail: bressloff@math.utah.edu and lawley@math.utah.edu

Received 5 January 2017, revised 12 March 2017
Accepted for publication 24 March 2017
Published 6 April 2017

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 heterogeneity

(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

$$T := \int_0^t \Theta(X(\tau)) d\tau, \quad (1.1)$$
where $\Theta(X)$ denotes the Heaviside function. The occupation time $T$ is an example of a Brownian functional. Since $X(t)$, $t \geq 0$, 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

$$T := \int_0^t I_V(X(r)) \, dr,$$

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 labelled $n = 0, 1$ such that $n(t) \in \{0, 1\}$ evolves according to a two-state Markov chain, $0 \xrightarrow{\alpha} 1$, with the matrix generator

$$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, $0 \xrightarrow{\beta} 1$, with the matrix generator
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)

$$dX(t) = \sqrt{2D_n} \, dW(t),$$

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

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

$$P\{X(t) ∈ (x, x + dx), n(t) = n|x_0, n_0\} = p_n(x, t|x_0, n_0, 0)dx.$$ 

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

$$\frac{∂p_n}{∂t} = D_1 \frac{∂^2 p_n(x, t)}{∂x^2} + \sum_{m=0,1} A_{mm} p_m(x, t), \quad n = 0, 1. \quad (2.3)$$

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

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

Given the first passage time

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

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

$$T_k := \int_0^T I_{(a_k, a_{k+1})}(X(t))dt, \quad k = 0, \ldots, m - 1. \quad (2.6)$$

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

In this paper we are interested in calculating the mean residence times $τ^m_k(x_0)$, where

$$τ^m_k(x_0) = E_{x_0,m}[T_k], \quad (2.7)$$

with $T_k$ the residence time in the interval $(a_k, a_{k+1})$ and $E_{x_0,m}$ 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

$$τ^m_k(x_0) = \sum_{n=0,1} \int_{a_0}^{a_{k+1}} dx \int_0^∞ dt p_n(x, t|x_0, m, 0). \quad (2.8)$$

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

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

The associated boundary conditions are

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

It follows that $τ^m_k$ evolves according to

$$D_m \frac{∂^2 τ^m_k(x_0)}{∂x_0^2} + \sum_{n=0,1} A_{mn}^\top τ_n(x_0) = -I_{(a_k, a_{k+1})}(x). \quad (2.10)$$

supplemented by the boundary conditions

$$τ^m_k(0) = 0, \quad τ^m_k(L) = 0.$$
2.2. Probabilistic formulation

One could determine the mean residence times \( \tau^a_n \) 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 \( dX(t) = V(X)dt + \sqrt{2D}dW(t) \). 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 \( \Omega \) with \( \sigma \)-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

\[
\mathbb{E}(Y|X) = \int y \rho(y|X) dy,
\]

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 \( \sigma \)-algebra (instead of with respect to a random variable), see [13, 15]. The conditional expectation satisfies

\[
\mathbb{E}(\mathbb{E}(Y|X)) = \int \int y \rho(y|x) \rho(x) dx dy = \int y \rho_2(y,x) dx dy = \mathbb{E}(Y),
\]

where \( \rho_2 \) 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 \( \sigma \)-algebra generated by the stochastic process \( X \) up to time \( t \) then corresponds to sets of sample paths, realizations or trajectories \( \{X(s), 0 \leq s \leq t\} \). A stopping time \( \tau \) 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 \( \tau \leq t \), that is, knowledge of the sample path \( \{X(s), s \leq t\} \) is sufficient to determine whether or not \( \tau \leq t \). It immediately follows that the first passage time (2.5) is a stopping time. Given any stopping time \( \tau \) with respect to \( X \), if the stochastic process \( Y(t) = X(t + \tau) - X(\tau) \) is independent of \( \{X(s), s < \tau\} \) 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 \( n \in \{0, 1\} \),

\[
s_n^y := \inf \{t > 0 : \{X(t) = y\} \cap \{n(t) = n\}\}.
\]
For any stopping time \( S \), we denote the \( \sigma \)-algebra generated by the process \( \{(X(t), n(t))\}_{t=0}^{\infty} \) 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

\[
\tau_k^x(x) = E_{x,r}[\tau_k 1_{\tau_k < T} 1_{\tau_k < s_k}^x] + E_{x,r}[\tau_k 1_{\tau_k < T} 1_{\tau_k < s_k}^x | F(s_k)]
\]

\[
= E_{x,r}[\tau_k 1_{\tau_k < T} 1_{\tau_k < s_k}^x | F(s_k)]
\]

\[
+ E_{x,r}[\tau_k 1_{\tau_k < T} 1_{\tau_k < s_k}^x | F(s_k)]
\]

\[
= P_{x,r}(\{s_k^0 < T\} \cap \{s_k^1 < s_k^0\}) \tau_k^0(a_k)
\]

\[
+ P_{x,r}(\{s_k^1 < T\} \cap \{s_k^0 < s_k^1\}) \tau_k^1(a_k).
\]  

(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 \( T_k \) on the particle entering the interval \([a_k, a_{k+1}]\) is trivial when \( x < a_k \), since \( T_k = 0 \) 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

\[
\tau_k^x(x) = E_{x,r}[\tau_k 1_{\tau_k < T} 1_{\tau_k < s_k}^x] + E_{x,r}[\tau_k 1_{\tau_k < T} 1_{\tau_k < s_k}^x | F(s_k)]
\]

\[
= P_{x,r}(\{s_k^0 < T\} \cap \{s_k^1 < s_k^0\}) \tau_k^0(a_{k+1})
\]

\[
+ (1 - P_{x,r}(\{s_k^0 < T\} \cap \{s_k^1 < s_k^0\})) \tau_k^1(a_{k+1}).
\]  

(2.13)

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

\[
p_k^x(x) := P_{x,r}(\{s_k^0 < T\} \cap \{s_k^1 < s_k^0\}), \quad x \in [0, a_k]
\]

\[
\tilde{p}_k^x(x) := P_{x,r}(\{s_k^1 < T\} \cap \{s_k^0 < s_k^1\}), \quad x \in [0, a_k]
\]

\[
\tilde{q}_k^x(x) := P_{x,r}(s_k^0 < s_k^1), \quad x \in [a_{k+1}, a_m].
\]

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

\[
S_r(x) := \tau_k^0 + \tau_k^1, \quad \Delta_r := \tau_k^0 - \tau_k^1,
\]

with \( S_p, \Delta_p, S_b, \Delta_b, \) and \( S_q, \Delta_q \) defined analogously. In these new variables, (2.12) and (2.13) become

\[
S_r(x) = \begin{cases} \frac{1}{2}(S_p(x) + S_b(x))S_r(a_k) + \frac{1}{2}(S_p(x) - S_b(x))\Delta_r(a_k), & x \in [0, a_k] \\ S_r(a_{k+1}) + (S_q(x) - 1)\Delta_r(a_{k+1}), & x \in [a_{k+1}, a_m] \end{cases}
\]  

(2.14)

and

\[
\Delta_r(x) = \begin{cases} \frac{1}{2}(\Delta_p(x) + \Delta_b(x))S_r(a_k) + \frac{1}{2}(\Delta_p(x) - \Delta_b(x))\Delta_r(a_k), & x \in [0, a_k] \\ \Delta_q(x)\Delta_r(a_{k+1}), & x \in [a_{k+1}, a_m] \end{cases}
\]  

(2.15)

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

\[
L \Delta_p = \Gamma \Delta_p = 0,
\]  

(2.16a)
\[ L \Delta_p - \Gamma \Delta_p = 0, \quad (2.16b) \]

where
\[ L := \frac{d^2}{dx^2}, \quad \Gamma_{\pm} := \frac{D_1 \beta \pm D_0 \alpha}{D_1 D_0}, \quad (2.17) \]

with boundary conditions
\[ \Delta_p(a_0) = S_p(a_0) = 0, \quad \Delta_p(a_k) = S_p(a_k) = 1. \quad (2.18) \]

Further, \( \Delta_{\tilde{p}} \) and \( S_{\tilde{p}} \) satisfy (2.16a) and (2.16b) 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
\[ \Delta_{\tilde{p}} = -\Delta_p, \quad (2.19) \]

and thus
\[ L(S_p + S_{\tilde{p}}) = 0 \]
\[ L(S_p - S_{\tilde{p}}) - 2\Gamma \Delta_p = 0, \quad (2.20a) \]

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, \( \Delta_q \) and \( S_q \) satisfy (2.16a) and (2.16b) 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 \( \Delta_p, S_p + S_{\tilde{p}}, S_p - S_{\tilde{p}}, \Delta_q, \) and \( S_q \). Setting \( a_j = j/l \) for each \( j \in \{0, 1, \ldots, m\} \), we have
\[ \Delta_p(x) = \operatorname{csch}(\sqrt{\Gamma + kl}) \sinh(\sqrt{\Gamma} x), \]
\[ (S_p + S_{\tilde{p}})(x) = 2x/(kl), \]
\[ (S_p - S_{\tilde{p}})(x) = \frac{2\Gamma - [kl \sinh(\sqrt{\Gamma} x) \csc(\sqrt{\Gamma} kl) - x]}{\Gamma_{\pm} kl}, \]
\[ \Delta_q(x) = \operatorname{sech}(\sqrt{\Gamma + (m - (k + 1))l}) \cosh(\sqrt{\Gamma + (m l - x)}), \]
\[ S_q(x) = \frac{\Gamma - (\Delta_q(x) - 1) + 1}{\Gamma_{\pm}}. \]

It remains to determine \( \Delta_\tau \) and \( S_\tau \) on \( [a_k, a_{k+1}] \). Again, following our previous work [3, 4, 7] one can show that \( \Delta_\tau \) and \( S_\tau \) satisfy the following ODEs on \( (a_k, a_{k+1}) \)
\[ L \Delta_\tau - \Gamma_+ \Delta_\tau = -\gamma_- \]
\[ L S_\tau - \Gamma_- \Delta_\tau = -\gamma_+ \]

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

\[ \Delta_\tau(a_k) = S_\tau(a_k) = 0, \]
\[ \Delta_\tau(a_{k+1}) = S_\tau(a_{k+1}) = 1. \]

Similarly, \( \Delta_\tau \) and \( S_\tau \) satisfy (2.16a) and (2.16b) on \( (a_{k+1}, a_m) \) with boundary conditions
\[ (S_\tau + S_{\tilde{\tau}})(a_0) = 0, \quad (S_\tau + S_{\tilde{\tau}})(a_k) = 2 \]
\[ (S_\tau - S_{\tilde{\tau}})(a_0) = 0, \quad (S_\tau - S_{\tilde{\tau}})(a_k) = 0. \]
\begin{equation}
S'_{\gamma}(a_k) = \frac{1}{2}(S'_{\gamma}(a_k) + S'_{\gamma}(a_k))S_{\gamma}(a_k) + \frac{1}{2}(S'_{\gamma}(a_k) - S'_{\gamma}(a_k))\Delta_{\gamma}(a_k)
\end{equation}
\begin{equation}
\Delta'_{\gamma}(a_k) = \Delta'_{\gamma}(a_k)\Delta_{\gamma}(a_k)
\end{equation}
\begin{equation}
S'_{\gamma}(a_{k+1}) = S'_{\gamma}(a_{k+1})\Delta_{\gamma}(a_{k+1})
\end{equation}
\begin{equation}
\Delta'_{\gamma}(a_{k+1}) = \Delta'_{\gamma}(a_{k+1})\Delta_{\gamma}(a_{k+1}).
\end{equation}

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 \(S_{\gamma}\) and \(\Delta_{\gamma}\). In particular, with \(a_j = j\ell\) for each \(j \in \{0, 1, \ldots, m\}\), we have that
\begin{equation}
\Delta_{\gamma}(x) = \frac{\gamma_{-}}{\Gamma_{+}} - \frac{\gamma_{-}}{2\Gamma_{+}}\text{sech}\left(\sqrt{\Gamma_{+}m}\ell\right)\left[cosh\left(\sqrt{\Gamma_{+}}((k + 1)\ell - x)\right)
+ cosh\left(\sqrt{\Gamma_{+}}((k + 1)\ell + x)\right) - cosh\left(\sqrt{\Gamma_{+}}((k + 1)\ell + x)\right)\right],
\end{equation}
\begin{equation}
S_{\gamma}(x) = \frac{e^{-\sqrt{\Gamma_{+}}(2k\ell + x)}}{4\Gamma_{+}m}\left[2e^{\sqrt{\Gamma_{+}}(2k\ell + x)}\left(\gamma_{-}\Gamma_{+}(k^2\ell^2 - 2(k + 1)\ell x + x^2) + 2\right)
\right.
- \gamma_{-}\Gamma_{+}^2(k^2\ell^2 - 2(k + 1)\ell x + x^2)
\left.
+ \gamma_{-}\Gamma_{+}(e^{\sqrt{\Gamma_{+}l}} - 1)e^{\sqrt{\Gamma_{+}l}}\left((e^{\sqrt{\Gamma_{+}l}}) + e^{2\sqrt{\Gamma_{+}l}} - 1\right)\tan(\sqrt{\Gamma_{+}ml})\right.
\right.
\left.
+ \text{sech}\left(\sqrt{\Gamma_{+}ml}\right)e^{\sqrt{\Gamma_{+}l}} - 1\right)
\right.
\left.
- \gamma_{-}\Gamma_{+}(e^{\sqrt{\Gamma_{+}l}}) + e^{\sqrt{\Gamma_{+}l}}(e^{2\sqrt{\Gamma_{+}l}}) + e^{\sqrt{\Gamma_{+}l}}(3k\ell + x)\right].
\end{equation}

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,
\begin{equation}
P(n(t) = 0) = \rho_0 := \frac{\alpha}{\alpha + \beta}; \quad P(n(t) = 1) = \rho_1 := \frac{\beta}{\alpha + \beta},
\end{equation}
and set \(\tau_k = \rho_0\tau^0_k + \rho_1\tau^1_\ell\). Thus all of our numerical results will be in terms of \(\tau_k\) rather than the components \(\tau^0_k\). 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 \(l = 1 \mu m\) and \(\alpha = 1 \text{ s}^{-1}\) so that \(D\) varies between 0.01–10 \(\mu m^2 \text{ s}^{-1}\).

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
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 $x \in [a_k, a_{k+1}]$. 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

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

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

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

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

\[ dX(t) = D_n \frac{d-1}{X(t)} \, dt + \sqrt{2D_n} \, dW(t), \]  

(2.26)

when $n(t) = n \in \{0, 1\}$. As in section 2.2, we would like to compute the expected value of $T_k$ as a function of starting position with $T_k$ 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

\[ \mathcal{L} := \frac{d}{x} \frac{d}{dx} + \frac{d^2}{dx^2}, \quad \Gamma \pm := \frac{D_1 \beta \pm D_0 \alpha}{D_1 D_0}. \]  

(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 $k$th 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 $k$th 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 $k$th 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 (2.28a)–(2.28c). 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.)
\[ S_k(1) = (k + 1)l - kl = l \]  \hspace{1cm} (2.28a)

\[ S_k(2) = \pi(a_0 + (k + 1)l)^2 - \pi(a_0)^2 \approx k \]  \hspace{1cm} (2.28b)

\[ S_k(3) = \frac{4}{3}\pi(a_0 + (k + 1)l)^3 - \frac{4}{3}\pi(a_0 + kl)^3 \approx k^2. \]  \hspace{1cm} (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 \( n(t) \in \{0, 1\} \).

\[ 0 \overset{\beta}{\longrightarrow} 1, \]

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 \( \bar{T}_k \) as a function of starting position, so we again decompose \( \tau_k = \rho_0 \bar{T}_k^0 + \rho_1 \bar{T}_k^1 \) with

\[ \tau_k^0(x) = E_{x,n}[\bar{T}_k]. \]

Define the splitting probability \( r_k^0 \) by

\[ r_k^0(x) = P_{x,n}(s^0_{a_k} < T), \]

where \( s^0_{a_k} \) 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

\[ \tau_k^0(x) = E_{x,n}[\bar{T}_k 1_{s^0_{a_k} < T}] = E_{x,n}[1_{s^0_{a_k} < T}E_{x,n}[\bar{T}_k|F(s^0_{a_k})]] \]

\[ = P_{x,n}(s^0_{a_k} < T)E_{a_k,0}[\bar{T}_k] = r_k^0(x)\tau_k^0(a_k). \]  \hspace{1cm} (3.1)

Further, if \( x > a_{k+1} \) then

\[ \tau_k^0(x) = E_{x,n}[E_{x,n}[\bar{T}_k|F(s^0_{a_{k+1}})]] = E_{x,n,0}[\bar{T}_k] \]

\[ = \tau_k^0(a_{k+1}). \]  \hspace{1cm} (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 \( x \in (a_i, a_{i+1}) \), then \( r_k^0(x) \) is an average of \( r_k^0(a_i) \) and \( r_k^0(a_{i+1}) \). By the strong Markov property,

\[ r_k^0(x) = P_{x,n}(s^0_{a_k} < T | s^0_{a_i} < s^0_{a_{i+1}})P_{x,n}(s^0_{a_i} < s^0_{a_{i+1}}) \]

\[ + P_{x,n}(s^0_{a_k} < T | s^0_{a_i} > s^0_{a_{i+1}})P_{x,n}(s^0_{a_i} > s^0_{a_{i+1}}) \]

\[ = P_{a_i,0}(s^0_{a_k} < T)P_{x,n}(s^0_{a_i} < s^0_{a_{i+1}}) \]

\[ + P_{a_{i+1},0}(s^0_{a_k} < T)P_{x,n}(s^0_{a_i} > s^0_{a_{i+1}}) \]

\[ = r_k^0(a_i)[1 - P_j^0(x)] + r_k^0(a_{i+1})P_j^0(x), \]
where \( p^j_j(x) := P_{x,s}(s^0_x > s^0_{x+1}) \). Following our previous work [3, 4, 7] one can show that \( p^j_j \) satisfies the following ODEs on \((a_j, a_{j+1})\)

\[
D_0 \mathcal{L} p^j_j + \beta (p^j_j - p^0_j) = 0, \quad (3.3a)
\]

\[
D_1 \mathcal{L} p^j_j + \alpha (p^j_j - p^j_0) = 0, \quad (3.3b)
\]

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

\[
p^j_0(a_j) = \frac{d}{dx} p^j_j(a_j) = \frac{d}{dx} p^j_j(a_{j+1}) = 0, \quad \text{and} \quad p^j_0(a_{j+1}) = 1.
\]

One can solve this boundary value problem explicitly and obtain explicit expressions for \( p^j_j \).

In dimension \( d = 1 \):

\[
p^j_0(x) = \frac{\beta D_1^{1/2} \sinh((-jl + l/2 + x)\Lambda) + \sinh(j\Lambda)}{2\beta D_1^{1/2} \sinh(j\Lambda) + \alpha \sqrt{D_0(D_0 + \beta D_1)} \cosh(j\Lambda)}
\]

\[
\frac{\alpha(-jl + l + x) \sqrt{D_0(D_0 + \beta D_1)} \cosh(j\Lambda)}{2\beta D_1^{1/2} \sinh(j\Lambda) + \alpha \sqrt{D_0(D_0 + \beta D_1)} \cosh(j\Lambda)},
\]

\[
p^j_1(x) = \frac{\sqrt{D_1} (\beta D_1 \sinh(j\Lambda) - \alpha D_0 \sinh((-jl + l/2 + x)\Lambda))}{2\beta D_1^{1/2} \sinh(j\Lambda) + \alpha \sqrt{D_0(D_0 + \beta D_1)} \cosh(j\Lambda)}
\]

\[
\frac{\alpha(-jl + l + x) \sqrt{D_0(D_0 + \beta D_1)} \cosh(j\Lambda)}{2\beta D_1^{1/2} \sinh(j\Lambda) + \alpha \sqrt{D_0(D_0 + \beta D_1)} \cosh(j\Lambda)},
\]

where

\[
\Lambda = \sqrt{\frac{\alpha}{D_1} + \frac{\beta}{D_0}}.
\]

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

\[
r^j_k(a_j) = (1 - Q_j) r^j_k(a_{j-1}) + Q_j r^j_k(a_{j+1}),
\]

where \( Q_j \) is found by solving a certain boundary value problem. In particular, \( Q_j = \tilde{q}^j_j(a_j) \) where \( \tilde{q}^j_j(x) \) satisfies

\[
D_0 \mathcal{L} \tilde{q}^j_j + \beta (\tilde{q}^j_j - \tilde{q}^0_j) = 0, \quad x \in (a_{j-1}, a_j),
\]

\[
D_1 \mathcal{L} \tilde{q}^j_j + \alpha (\tilde{q}^j_j - \tilde{q}^j_0) = 0, \quad x \in (a_{j-1}, a_j),
\]

with boundary conditions

\[
\frac{d}{dx} \tilde{q}^j_j(a_{j-1}) = \frac{d}{dx} \tilde{q}^j_j(a_j) = \frac{d}{dx} \tilde{q}^j_j(a_{j+1}) = \frac{d}{dx} \tilde{q}^j_j(a_{j+1}) = 0, \quad \tilde{q}^j_j(a_{j+1}) = 1,
\]

and continuity conditions

\[
\tilde{q}^j_j(0-) = \tilde{q}^j_j(0+), \quad \text{and} \quad \frac{d}{dx} \tilde{q}^j_j(a_j) = \frac{d}{dx} \tilde{q}^j_j(a_j).
\]
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 $\{r_k^0(a_j)\}_{j=1}^d$ 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,

$$r_k^0(a_j) = \frac{1}{k}.$$

Putting this together, we have that

$$\frac{d}{dx} r_k^0(a_k) = \frac{1}{k} \frac{d}{dx} \rho_k^0(a_k).$$

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

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

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

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

$$(3.8c) \quad \frac{d}{dx} \tau_k^0(a_k) = \tau_k^0(a_k) \frac{d}{dx} r_k^0(a_k) = \tau_k^0(a_k) \frac{1}{k} \frac{d}{dx} \rho_k^0(a_k),$$

$$(3.8d) \quad \frac{d}{dx} \tau_k^1(a_k) = 0,$$

$$(3.8e) \quad \frac{d}{dx} \tau_k^1(a_{k+1}) = 0.$$

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

$$\tau_k(x) = \frac{1}{2A \alpha D_0 (\alpha + \beta) (\alpha D_0 + \beta D_1)^2} \left[ 2A \beta l (\alpha + \beta) \sqrt{D_0 D_1 (\alpha D_0 + \beta D_1)} \right. $$

$$+ D_1 (\alpha + \beta) \cosh(l \Lambda) \cos \left( \left[ (k + 1) l - x \right] \Lambda \right)$$

$$+ \left. D_1 (\alpha + \beta) \coth(l \Lambda) \right] - (\alpha D_0 + \beta D_1)$$

$$+ \left. \left( A_0 D_0 \left( \alpha^2 (k l - x) ((k + 2) l - x) + 2 \beta (\alpha (k - x) ((k + 2) l - x) - D_0 + D_1) \right. \right. \right.$$

$$\left. + \beta^2 (k l- x) ((k + 2) l - x) - 2 l (\alpha + \beta)^2 (\alpha D_0 + \beta D_1) \right] \right],$$

where $A = \frac{1}{k} \frac{d}{dx} \rho_k^0(a_k)$ and $\rho_k^0$ 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
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.

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 $\alpha = \beta = 0$, the green curve has $\alpha = \beta = 1$, the red curve has $\alpha = \beta = 100$. (Smaller amplitude solid curves correspond to faster switching rates.)
There are a number of possible extensions of our work. One 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

PCB was supported by the National Science Foundation (DMS-1613048). SDL was supported by the National Science Foundation (DMS-RTG 1148230).

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

\[
J_n(x, y) = I_n(\sqrt{x} y) K_n(\sqrt{x} y).
\]

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

\[
\Delta_n(x) = \frac{f_{00}(x, a_0) - f_{00}(a_0, x)}{f_{00}(a_0, a_0) - f_{00}(a_0, a_1)}
\]

\[
\langle S_p + S_q \rangle(x) = \frac{2 \log \left( \frac{x}{a_0} \right)}{\log \left( \frac{x}{a_0} \right)}
\]

\[
\langle S_p - S_q \rangle(x) = \frac{2 \Gamma - \left( \log \left( \frac{x}{a_0} \right) f_{00}(a_0, a_0) + \log \left( \frac{a_0}{x} \right) f_{00}(a_0, x) + \log \left( \frac{a_0}{x} \right) f_{00}(x, a_0) + \log \left( \frac{x}{x} \right) f_{00}(a_0, a_0) \right)}{\Gamma \log \left( \frac{a_0}{x} \right) (f_{00}(a_0, a_0) - f_{00}(a_0, a_1))}
\]

\[
\Delta_q(x) = \frac{f_{00}(a_0, x) + f_{01}(x, a_0)}{f_{00}(a_0, a_0) + f_{01}(a_0, a_0)}
\]

\[
S_q(x) = \frac{(\Gamma - \Gamma_j) [f_{01}(a_0, a_0) + f_{01}(a_0, a_0)] + \Gamma_j [f_{00}(a_0, x) + f_{01}(a_0, a_0)]}{\Gamma_j [f_{00}(a_0, a_0) + f_{01}(a_0, a_0)]}
\]

\[
\Delta_x(x) = \frac{\sqrt{\Gamma \left[ F_1(x) + \tilde{F}_1(x) - G_1(x) + \tilde{G}_1(x) \right] + \gamma_j [f_{00}(a_0, a_0) + f_{01}(a_0, a_0)]}}{\Gamma_j [f_{00}(a_0, a_0) + f_{01}(a_0, a_0)]}
\]

where

\[
F_1(x) = \gamma_j f_{01}(a_0, x)[a_k + f_{01}(a_0, a_0)] - a_k f_{01}(a_0, a_1)
\]

\[
\tilde{F}_1(x) = \gamma_j [f_{01}(x, a_0)[a_k + f_{01}(a_0, a_0)] - a_k f_{01}(a_0, a_0)]
\]

\[
G_1(x) = \gamma_j f_{01}(a_0, a_0)[a_k f_{01}(a_0, x) + a_k + f_{01}(x, a_0)]
\]

\[
\tilde{G}_1(x) = \gamma_j f_{01}(a_0, a_0)[a_k f_{01}(a_0, x) + a_k + f_{01}(a_0, x)].
\]
and
\[
S_\tau(x) = \left[ f_1(a_0, a_m) + f_0(a_m, a_0) \right] [H_k(x) + 4a_k \gamma \Gamma_\tau - (f_1(a_k, a_0) + f_0(a_k, a_0))]
\]
\[
+ 4\Gamma_\tau \left( F_k(x) + \tilde{F}_k(x) - G_k(x) - \tilde{G}_k(x) \right) \left( 41^{3/2} (f_1(a_m, a_0) + f_0(a_0, a_m)) \right)^{-1},
\]
where
\[
H_k(x) = \left( -2a_k \gamma \Gamma_\tau \sqrt{\gamma} \log \left( \frac{a_0}{a_k} \right) + 2a_k^2 \gamma^2 \Gamma_\tau \log \left( \frac{a_0}{a_0} \right) + 2a_k^2 a_k^2 \Gamma_\tau \sqrt{\gamma} \log \left( \frac{a_k}{a_k} \right) \right.
\]
\[
- 2a_k^2 a_k^2 \Gamma_\tau \log \left( \frac{a_k}{a_k} \right) - a_k^2 \gamma \Gamma_\tau \gamma \sqrt{\gamma} \Gamma_\tau \log \left( \frac{a_0}{a_0} \right) + 2a_k^2 \gamma \Gamma_\tau \gamma \sqrt{\gamma} \Gamma_\tau \log \left( a_0 \right) - 2a_k^2 \gamma \Gamma_\tau \gamma \sqrt{\gamma} \Gamma_\tau \log \left( a_k \right)
\]
\[
- 2a_k^2 \gamma \Gamma_\tau \gamma \sqrt{\gamma} \Gamma_\tau \log \left( x \right) + 2a_k^2 \gamma \Gamma_\tau \gamma \sqrt{\gamma} \Gamma_\tau \log \left( x \right) + \gamma \Gamma_\tau \sqrt{\gamma} \gamma \sqrt{\gamma} \Gamma_\tau \log \left( x \right).
\]

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