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A PROBABILISTIC ANALYSIS OF VOLUME TRANSMISSION IN THE BRAIN*

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Abstract. Volume transmission is a fundamental neural communication mechanism in which neurons in one brain nucleus modulate the neurotransmitter concentration in the extracellular space of a second nucleus. In this paper, we formulate and analyze a mathematical model of volume transmission to calculate the neurotransmitter concentration in the extracellular space. Our model consists of the diffusion equation in a bounded two- or three-dimensional domain that contains a set of interior holes that randomly switch between being either sources or sinks. The interior holes represent nerve varicosities that are sources of neurotransmitter when firing an action potential and are sinks otherwise. To analyze this random partial differential equation, we show that each realization of its solution can be represented as a certain expected local time of a Brownian particle in a corresponding realization of a random environment. Using this representation, we prove two surprising results. First, the expected neurotransmitter concentration is approximately constant across the extracellular space. Second, by computing an explicit formula for this constant, we find that it depends on very few details in the problem. In particular, this constant does not depend on the number or arrangement of nerve varicosities, the geometry or size of the extracellular space, or firing correlations between neurons. The biological implications of these results will be explored in a forthcoming paper.

Key words. stochastic switching, volume transmission, neuromodulation, stochastic hybrid system, random PDE, piecewise deterministic Markov process, randomly switching boundary

AMS subject classifications. 35R60, 60K37, 60J60, 60H15, 92C20

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1. Introduction.

Classical one-to-one *synaptic transmission* is a fundamental mechanism by which neurons convey information. In synaptic transmission, a neuron fires an action potential to convey an electrical signal to an adjacent neuron. Mathematical analysis of this mode of neural communication is one of the best examples of mathematics providing deep biological insight [21, 39]. In addition, modeling this neural process has benefited the field of mathematics, having stimulated a tremendous amount of dynamical systems theory (see [17] and the references therein).

But in addition to synaptic transmission, there is another fundamental neural communication mechanism known as *volume transmission* [3, 18, 19, 20, 38]. In volume transmission, sets of neurons project to a distant brain volume and when they fire they increase the neurotransmitter concentration in the extracellular space in the distant volume [20]. Volume transmission is also called *neuromodulation* because it modulates synaptic transmission by other neurons or synapses in the projection region. Examples of volume transmission include the dopamine projection from the substantia nigra to the striatum [13], the serotonin projection from the dorsal raphe nucleus to the striatum [4, 5], and the norepinephrine projection from the locus coeruleus to the cortex [20]. This mechanism is critical to the sleep/wake cycle, motor control, and treating Parkinson's disease and various psychiatric disorders [20]. Despite its biological importance, very little mathematics has been applied to volume transmission.

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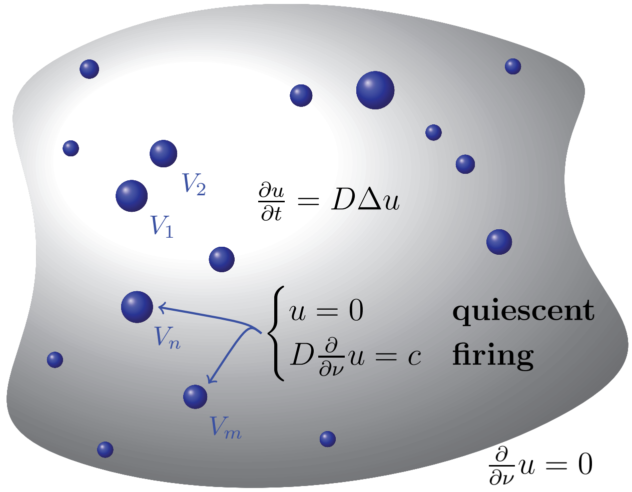

FIG. 1. *Model schematic. The grey region, $U \subset \mathbb{R}^3$, contains N nerve varicosities, $V_n \subset U$, $n = 1, \ldots, N$, depicted by small blue spheres. The neurotransmitter concentration, $u(x,t)$, satisfies the diffusion equation in the extracellular space, $E = U \backslash \overline{\cup_{n=1}^N V_n}$, with boundary conditions at nerve varicosities that randomly switch between absorption and flux into the space, corresponding to neurons that switch between quiescent and firing states. A no flux condition is imposed at the outer boundary.*

In this paper, we propose and analyze a mathematical model of volume transmission. Consider a collection of neurons that project to a distant volume where they release neurotransmitter through varicosities in the extracellular space. Each nerve varicosity in the projection region is a source of neurotransmitter when the neuron fires and is a sink for neurotransmitter when the neuron is not firing because neurotransmitter is taken back into the varicosity (see Figure 1). Given neural firing statistics, what is the average neurotransmitter concentration in the extracellular space? How does this average depend on spatial location, and the many parameters in the problem such as amount of neurotransmitter released when firing, the number of nerve varicosities, the arrangement of nerve varicosities, the size and geometry of the extracellular space, the neurotransmitter diffusion coefficient, etc.?

We answer these questions in the case that the size of nerve varicosities is small compared to the distance between nerve varicosities (see the discussion for the biological justification of this parameter regime). In this case, we prove that the expected neurotransmitter concentration is approximately constant across the extracellular space. Furthermore, we compute an explicit formula for this constant, and our formula shows that it depends on very few details in the problem. In particular, this constant does not depend on the number or arrangement of nerve varicosities, the geometry or size of the extracellular space, or firing correlations between neurons. The biological implications of these results will be explored in a forthcoming paper.

Mathematically, our model consists of the diffusion equation in a bounded two- or three-dimensional domain that contains a set of interior holes that randomly switch between being either sources or sinks. To analyze this random partial differential equation (PDE), we show that each realization of its solution can be represented as a certain expected local time of a Brownian particle in a corresponding realization of a random environment. This probabilistic particle perspective is the key that allows us to show that the expected random solution is approximately constant in space and to compute this constant.

We now comment on how this investigation relates to previous work. In [24], we used the mathematical methods developed in [26, 9, 23] to prove that the expected neurotransmitter concentration is exactly constant in one space dimension. In order to analyze the higher-dimensional problem in this paper, we introduce a local time representation of the solution to the random PDE. Our local time analysis in section 4.3 gives a probabilisitic interpretation of matched asymptotic analysis of elliptic and parabolic PDEs [15, 27, 36] (see Remark 17). More broadly, this investigation adds to the growing body of work on diffusion in random environments [25, 10, 6, 2, 11, 12] that has been driven by biological applications. Such processes combine two levels of randomness: Brownian motion at the individual particle level with a random environment.

The rest of the paper is organized as follows. In section 2, we briefly describe our model and give our main results. In section 3, we formulate a dimensionless version of our model precisely and prove that the neurotransmitter concentration (the solution to a random PDE) can be represented as a certain expected local time of a Brownian particle in a random environment (Theorems 1 and 3). In section 4, we use this local time representation to investigate the expected neurotransmitter concentration (Theorems 5, 6, and 15). We conclude by discussing parameter estimates from the neuroscience literature, higher order neurotransmitter statistics (such as variance), and future work. An appendix collects the proofs of several lemmas.

2. Basic problem setup and main results. Suppose $u(x,t)$ satisfies the diffusion equation

$$\frac{\partial u}{\partial t} = D\Delta u, \quad x \in E,\ t > 0,$$

where $u(x,t)$ is the concentration of some neurotransmitter in the extracellular space $E \subset \mathbb{R}^d$ (with $d = 2$ or 3) in some region of the brain. We suppose that a collection of neurons project to this region, and thus the domain E contains N holes in its interior, which represent the corresponding nerve varicosities; see Figure 1 (these are not the varicosities that occur in injured axons, also known as focal axonal swellings [28, 29, 30]). We assume that each varicosity is a ball centered at a point $x_n \in E$.

Each of the neurons fires action potentials and thus switches between a quiescent state and a firing state. We model neuron firing as a stochastic process, and we allow the neurons to fire synchronously, independently, or with some nontrivial correlations. When a neuron is firing, it releases neurotransmitter. When a neuron is not firing (quiescent), it absorbs neurotransmitter. Thus, we impose randomly switching boundary conditions at each nerve varicosity,

$$\begin{aligned} u(x,t) &= 0, && x \in \partial V_n, && \text{if neuron } n \text{ is quiescent at time } t,\\ D\tfrac{\partial}{\partial \nu} u(x,t) &= c > 0, && x \in \partial V_n, && \text{if neuron } n \text{ is firing at time } t, \end{aligned}$$

where ∂V_n is the boundary of the nth nerve varicosity and ν is the outward pointing unit normal vector. We suppose that neurotransmitter cannot escape the region through the outer boundary, and so we impose a no flux boundary condition there, $\frac{\partial}{\partial \nu} u(x,t) = 0$, if $x \in \partial E \backslash \cup_{n=1}^{N} \partial V_n$.

We thus have the diffusion equation with boundary conditions at interior holes that randomly switch between being sinks and sources. In this paper, we prove that the solution, $u(x,t)$, to this random PDE is a certain expected local time of a Brownian particle in a random environment (see Theorem 1 for a precise statement). The local time of a particle is the amount of time that the particle spends on a boundary.[1]

Using this representation, we prove that the large time mean, $\lim_{t\to\infty}\mathbb{E}[u(x,t)]$, exists and investigate its behavior in the case that the nerve varicosities are small compared to the distance between nerve varicosities (see the discussion for the biological justification of this parameter regime). That is, if $\mathbf{R}=(R_1,\dots,R_N)$ are the radii of the nerve varicosities and $l>0$ characterizes the distance between varicosities, then we introduce a small dimensionless parameter, $\varepsilon=\frac{1}{N}\sum_{n=1}^N R_n/l>0$. If neuron firing is controlled by an irreducible Markov process, $J(t)\in\{0,1\}^N$, then

$$\lim_{t\to\infty}\mathbb{E}[u(x,t)]\sim\kappa\frac{c}{D},\quad \text{as } \varepsilon\to 0, \tag{1}$$

where the constant κ is independent of x and depends on very few of the details in the problem. Throughout this paper, "$f\sim h$ as $\varepsilon\to 0$" means $f/h\to 1$ as $\varepsilon\to 0$.

If each component J_n of J is itself a Markov process with invariant measure, $\mathbb{P}(J_n(0)=0)=\rho_0^{(n)}$ and $\mathbb{P}(J_n(0)=1)=\rho_1^{(n)}$, then we compute κ explicitly and find

$$\kappa(d,\rho,\mathbf{R})=\frac{\sum_{n=1}^N\rho_1^{(n)}R_n g_d(R_n)}{\sum_{n=1}^N\rho_0^{(n)}R_n},$$

where g_d depends on the spatial dimension d,

$$g_d(R)=\begin{cases}-R\log R & \text{if } d=2,\\ R & \text{if } d=3.\end{cases} \tag{2}$$

Hence, if all the varicosities have the same radii and same invariant measure ($R_n=R$ and $\rho_1^{(n)}=\rho_1=1-\rho_0$ for all n), then

$$\kappa(d,\rho_1,R)=g_d(R)\frac{\rho_1}{\rho_0}.$$

Thus, κ depends *only* on (1) the spatial dimension, (2) the proportion of time each neuron is firing, and (3) the nerve varicosity radii. In particular, κ does *not* depend on (1) the spatial location, $x\in E$, (2) the number of varicosities, N, (3) the location of the varicosities, $\{x_1,\dots,x_N\}\in E$, (4) the size or shape of the extracellular space, E, or (5) any possible correlations between components of J. Thus, the mean neurotransmitter concentration is approximately constant in space and this constant is independent of much of the geometry and other details in the problem. In fact, the problem of N varicosities arranged arbitrarily in a general domain becomes equivalent to the case of a single varicosity placed in the center of a spherical domain. Figure 2 illustrates this result.

3. The neurotransmitter concentration is an expected local time in a random environment.

3.1. Setup and assumptions. We now give a precise and dimensionless version of the model described in section 2. For dimension $d\in\{2,3\}$, let $U\subset\mathbb{R}^d$ be open, connected, and bounded with a C^∞ boundary, ∂U. Let

$$V_n:=\{x\in U:|x-x_n|<\varepsilon r_n\},\quad n\in\{1,\dots,N\},$$

[1]For more information on local time, see sections I.11–I.12 in [1] or Chapter 6 in [22].

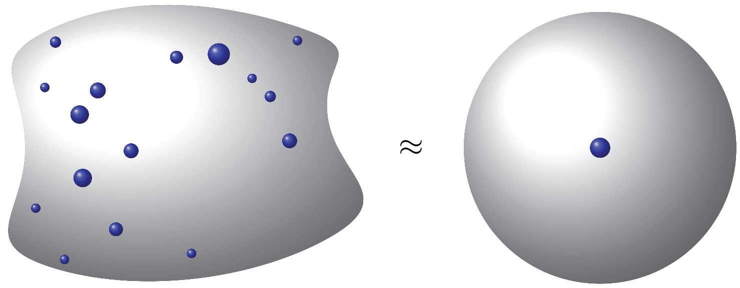

FIG. 2. *If the nerve varicosities are small, then Theorem* 15 *gives that the problem on the left with N varicosities arranged arbitrarily in a general domain is equivalent to the problem on the right of a single varicosity placed in the center of a spherical domain. For the problem on the right, the expected neurotransmitter concentration is exactly constant (even for non-Markovian neural firing) and we can compute this constant exactly if the firing is Markovian (see Theorem* 5 *and Corollary* 7*).*

be N balls of dimensionless radius $\varepsilon r_n > 0$ centered at $\{x_1, \dots, x_N\} \subset U$ in order to represent N nerve varicosities. Let $\varepsilon > 0$ be sufficiently small so that $\overline{V_n} \cap \overline{V_m} = \emptyset$ if $n \neq m$ and $\overline{V_n} \cap \partial U = \emptyset$ for each n. Let $E := U \backslash \overline{\cup_{n=1}^N V_n}$ be the extracellular space.

To describe the state of each neuron (either firing or quiescent), let $\{J(t)\}_{t\in\mathbb{R}}$ be a stochastic process on a probability space $(\Omega, \mathcal{F}, \mathbb{P})$ taking values in $\{0,1\}^N$, where $J_n(t) \in \{0,1\}$ denotes its nth component for $n \in \{1, \dots, N\}$. We assume that J takes only finitely many jumps in any bounded time interval. We assume that J is stationary in the sense that for each finite collection $\{A_j\}_{j=1}^k$ with $A_j \in \{0,1\}^N$, and times $\{t_j\}_{j=1}^k$, we have that

$$\mathbb{P}\big(\cap_{j=1}^k \{J(t_j) \in A_j\}\big) = \mathbb{P}\big(\cap_{j=1}^k \{J(t_j + T) \in A_j\}\big) \quad \text{for all } T \in \mathbb{R}. \tag{3}$$

Further, we assume J satisfies the following mixing condition: there exists $n^* \in \{1, \dots, N\}$, $\sigma > 0$, and $q \in (0,1)$ such that if $\{t_j\}_{j=1}^k$ satisfy $|t_i - t_j| > \sigma$ if $i \neq j$, then

$$\mathbb{P}\big(\cap_{j=1}^k \{J_{n^*}(t_j) = 1\}\big) \leq q^k. \tag{4}$$

We note that (4) is satisfied if J is (for example) an irreducible Markov process.

For almost all realizations of J, suppose $\{u(x,t)\}_{t\geq 0}$ is the $L^2(E)$-valued stochastic process that satisfies the diffusion equation in E with a zero initial condition and a no flux condition at the outer boundary,

$$\frac{\partial u}{\partial t} = \Delta u, \quad x \in E, \ t > 0, \tag{5}$$

$$u = 0, \qquad x \in E, \ t = 0, \tag{6}$$

$$\frac{\partial u}{\partial \nu} = 0, \qquad x \in \partial U, \tag{7}$$

and boundary conditions at each V_n that switch according to $J_n(t)$,

$$u = 0, \quad x \in \partial V_n, \ \text{if } J_n(t) = 0, \tag{8}$$

$$\frac{\partial u}{\partial \nu} = 1, \quad x \in \partial V_n, \ \text{if } J_n(t) = 1. \tag{9}$$

Here, $\nu(x)$ denotes the outward pointing unit normal vector at $x \in \partial E$. To get this dimensionless version of the model in section 2, one rescales time, space, and concentration, $\frac{D}{l^2}t$, $\frac{1}{l}x$, and $l^d u$, for some length scale, $l > 0$. Under this rescaling, the inhomogeneous flux condition becomes $l^{d+1}\frac{c}{D}$, but we have taken this to be 1 in (9) without loss of generality.

On the same probability space $(\Omega, \mathcal{F}, \mathbb{P})$, let $\{X(t)\}_{t\geq 0}$ be the path of a particle diffusing in $\overline{E}$ with reflecting boundary conditions,

$$dX(t) = \sqrt{2}\, dW(t) - \nu(X(t))\,(d\tilde{L}(t) + dL(t)), \quad X(t) \in \overline{E}. \tag{10}$$

Here, $W(t)$ is a d-dimensional Brownian motion, $\tilde{L}(t)$ is the local time of $X(t)$ on ∂U, and $L(t)$ is the local time of $X(t)$ on $\cup_{n=1}^{N}\partial V_n$. That is, $\tilde{L}(t)$ and $L(t)$ are nondecreasing continuous processes that increase only when $X(t) \in \partial U$ and $X(t) \in \cup_{n=1}^{N}\partial V_n$, respectively. We assume that X and J are independent.

3.2. Random PDE solution is an expected local time in a random environment. The following theorem relates the local time, L, of the particle, X, to the solution, $u(x,t)$, of the random PDE in (5)–(9). In the following, let $\mathbb{E}_x$ denote the expected value conditioned on $X(0) = x \in \overline{E}$ and $\mathbb{E}_x[\,\cdot\,|J]$ denote the expected value conditioned on $X(0) = x \in \overline{E}$ and a realization $J = \{J(t)\}_{t\in\mathbb{R}}$. We also use $\wedge$ to denote the minimum of two real numbers, i.e., $a \wedge b = \min\{a, b\}$.

THEOREM 1. *For $T \geq 0$, let $\tau(T)$ be the first passage time of $X(t)$ to some ∂V_n when $J_n(T-t) = 0$,*

$$\tau(T) := \inf\{t > 0 : (X(t) \in \partial V_n) \text{ and } (J_n(T-t) = 0) \text{ for some } n \in \{1, \dots, N\}\}. \tag{11}$$

Then for $x \in \overline{E}$ and almost all realizations of J, we have that

$$u(x,T) = \mathbb{E}_x[L(\tau(T) \wedge T)|J]. \tag{12}$$

Remark 2. We emphasize that there are two sources of randomness in (12): the path of the particle X, and the switching environment, J. Equation (12) is an average over paths of the particle for a given realization of the environment. Thus, (12) is a function of the realization J.

Proof. By standard properties of the diffusion equation, for almost all realizations of J, we have that $u(x, T-t)$ is smooth in x and t for t away from jump times of $\{J(T-t)\}_{0\leq t\leq T}$. Letting $0 = t_0 < t_1 < \cdots < t_{K-1} < t_K = T$ be all such jump times for a realization J, we apply Ito's formula[2] to obtain

$$\begin{aligned}
&\sum_{k=1}^{K}\Big(u(X(\tau(T)\wedge t_k), T-\tau(T)\wedge t_k^-) - u(X(\tau(T)\wedge t_{k-1}), T-\tau(T)\wedge t_{k-1}^+)\Big)\\
&\quad = -\sum_{k=1}^{K}\int_{\tau(T)\wedge t_{k-1}}^{\tau(T)\wedge t_k}(\nabla u\cdot\nu)(X(s))\,dL(s) + M\\
&\quad = -L(\tau(T)\wedge T) + M,
\end{aligned} \tag{13}$$

where M satisfies $\mathbb{E}_x[M|J] = 0$. We have used (5) and (7) in the first equality in (13), and we have used (9) and (11) in the second equality.

[2]Ito's formula is a fundamental result in stochastic analysis and is the stochastic counterpart to the chain rule [33].

Since $u(x,t)$ is continuous in t if $x \notin \cup_{n=1}^{N} \partial V_n$, and since the probability that $X(t_k) \in \cup_{n=1}^{N} \partial V_n$ is zero for $k \in \{0, 1, \dots, K\}$, taking the expectation of (13) over realizations of the particle X yields

$$\mathbb{E}_x[u(X(\tau(T) \wedge T), T - \tau(T) \wedge T)|J] - u(x,T) = -\mathbb{E}_x[L(\tau(T) \wedge T)|J]. \tag{14}$$

Using (6), (8), and (11), we have that (14) simplifies to (12). ∎

In general, the large T limit of (12) does not exist. However, we can average (12) over realizations of J and then take the large T limit. In light of (3), we henceforth write τ instead of $\tau(T)$ under expectations not conditioned on a realization of J.

THEOREM 3. *For each $x \in \overline{E}$, we have that*

$$\lim_{T \to \infty} \mathbb{E}[u(x,T)] = \mathbb{E}_x[L(\tau)] < \infty.$$

Before proving this theorem, we need the following lemma (see the appendix for the proof of the lemma).

LEMMA 4. *We have that* $\sup_{x \in \overline{E}} \mathbb{E}_x[\tau] < \infty$.

Proof of Theorem 3. By Lemma 4, we have that $\tau(0)$ is finite almost surely. Thus, $\lim_{T\to\infty} \tau(0) \wedge T = \tau(0)$ almost surely. Since the local time $L(t)$ is continuous, we have that $\lim_{T\to\infty} L(\tau(0) \wedge T) = L(\tau(0))$ almost surely. Furthermore, since $L(t)$ is nondecreasing, the monotone convergence theorem yields

$$\lim_{T \to \infty} \mathbb{E}_x[L(\tau(0) \wedge T)] = \mathbb{E}_x[L(\tau(0))]. \tag{15}$$

Combining (15) with (12) and the fact that $\mathbb{E}_x[L(\tau(0) \wedge T)] = \mathbb{E}_x[L(\tau(T) \wedge T)]$ by (3) completes the proof. ∎

4. Mean neurotransmitter.

4.1. Exactly constant in simple geometries. Before moving to general domains with an arbitrary number of nerve varicosities in section 4.3, we first consider the case of a single varicosity located in the center of a radially symmetric domain. Though this may seem like a very special case at first, we show in section 4.3 that all cases reduce to this one if the nerve varicosities are small.

In light of Theorem 3, we easily obtain the following theorem.

THEOREM 5. *Let U be an open ball of radius $\delta > 0$ with an open ball, V_1, of radius $\varepsilon \in (0, \delta)$ located at its center:*

$$U := \{x \in \mathbb{R}^d : |x| < \delta\} \quad \textit{and} \quad V_1 := \{x \in \mathbb{R}^d : |x| < \varepsilon\}.$$

Then $\lim_{T\to\infty} \mathbb{E}[u(x,T)]$ *is independent of* $x \in \overline{U \backslash V_1}$.

Proof. The theorem follows immediately from Theorem 3, the strong Markov property, and the fact that $L(t)$ only increases with $|X(t)| = \varepsilon$. ∎

4.2. A boundary value problem if switching is Markovian. If the jump process, J, is an irreducible Markov process, then we can write down the PDE boundary value problem that the mean neurotransmitter satisfies. For notational ease, let $\mathcal{J}$ index a partition, $\{A_j\}_{j \in \mathcal{J}}$, of the state space of J with

$$\mathbb{P}(J(0) = A_j) > 0 \text{ for each } j \in \mathcal{J} \quad \text{and} \quad \mathbb{P}(J(0) \in \cup_{j \in \mathcal{J}} A_j) = 1.$$

Note that the cardinality of $\mathcal{J}$ satisfies $2 \leq |\mathcal{J}| \leq 2^N$. Let $\rho \in \mathbb{R}^{|\mathcal{J}|}$ denote the invariant measure of J so that its jth component gives

$$\rho_j = \mathbb{P}(J(0) = A_j) \quad \text{for } j \in \mathcal{J}.$$

In particular, if $Q \in \mathbb{R}^{|\mathcal{J}|\times|\mathcal{J}|}$ denotes the generator matrix of J, then $Q^T\rho = 0$, where Q^T is the transpose of Q. Recall that the generator Q is the $|\mathcal{J}| \times |\mathcal{J}|$ matrix with nonnegative off diagonal entries $Q(i,j) \geq 0$ giving the jump rate from state $i \in |\mathcal{J}|$ to $j \in |\mathcal{J}|$ [32]. The diagonal entries of Q are chosen so that Q has zero row sums.

THEOREM 6. *Let J be an irreducible Markov process with generator $Q \in \mathbb{R}^{|\mathcal{J}|\times|\mathcal{J}|}$. Suppose $\boldsymbol{v} : \overline{E} \mapsto \mathbb{R}^{|\mathcal{J}|}$ is a vector valued function that satisfies*

$$\overline{0} = \Delta \boldsymbol{v} + Q^T \boldsymbol{v}, \quad x \in E, \tag{16}$$

and each component, v_j satisfies a reflecting boundary condition at the outer boundary,

$$\frac{\partial v_j}{\partial \nu} = 0, \quad x \in \partial U,\ j \in \mathcal{J}, \tag{17}$$

and boundary conditions at nerve varicosities,

$$v_j = 0, \quad x \in \partial V_n,\ \text{if } J_n = 0 \text{ when } J \text{ is in state } j \in \mathcal{J}, \tag{18}$$

$$\frac{\partial v_j}{\partial \nu} = \rho_j, \quad x \in \partial V_n,\ \text{if } J_n = 1 \text{ when } J \text{ is in state } j \in \mathcal{J}. \tag{19}$$

Then for each $x \in \overline{E}$ we have that

$$\lim_{T\to\infty} \mathbb{E}[u(x,T)] = \sum_{j\in\mathcal{J}} v_j(x).$$

Proof. Let $\mathbf{w}(x) \in \mathbb{R}^{|\mathcal{J}|}$ be defined by its jth component

$$w_j(x) = \frac{1}{\rho_j} v_j(x), \quad j \in \mathcal{J}. \tag{20}$$

If $\widetilde{Q} \in \mathbb{R}^{|\mathcal{J}|\times|\mathcal{J}|}$ denotes the generator of the time reversal of J, then its entries are related to the entries of Q by $\rho_j\widetilde{Q}(j,i) = \rho_i Q(i,j)$ (see, for example, section 3.7 in [32]). It is thus immediate that $\mathbf{w}$ satisfies the same boundary value problem as $\mathbf{v}$, but with $\widetilde{Q}$ replacing Q^T in (16), and 1 replacing ρ_j in (19).

Let $I(t) = J(-t)$ denote the time reversal of J. Let X be as in (10) and $\tau(0)$ be as in (11). Denote $w_j(x)$ by $w(x,j)$ and let $\mathbb{E}_{x,j}$ denote expectation conditioned on $X(0) = x$ and $I(0) = j$. By the generalized Ito formula,[3] we have that

$$\begin{aligned} &\mathbb{E}_{x,j}[w(X(t\wedge\tau(0)), I(t\wedge\tau(0)))] - w(x,j) \\ &\quad = \mathbb{E}_{x,j}\left[\int_0^{t\wedge\tau(0)} \left[\Delta w(X(s), I(s)) + \sum_{i\in\mathcal{J}} \tilde{Q}(I(s),i) w(X(s),i)\right] ds\right] \\ &\qquad - \mathbb{E}_{x,j}\left[\int_0^{t\wedge\tau(0)} \partial_\nu w(X(s), I(s))\,(dL(s) + dL^0(s))\right]. \end{aligned} \tag{21}$$

[3]Ito's formula is a fundamental result in stochastic analysis and is the stochastic counterpart to the chain rule [33]. Here, we use the generalized Ito formula which applies to SDEs with random switching. For more information, see Lemma 3 on p. 104 of [40] or Lemma 1.9 on p. 49 of [31].

By the PDE in (16) and the definition of $\mathbf{w}$ in (20), the first term on the right-hand side of (21) vanishes. By the boundary conditions in (17) and (19), the definition of $\mathbf{w}$, and the definition of $\tau(0)$, we then have that (21) becomes

$$w(x,j) = \mathbb{E}_{x,j}[L(t \wedge \tau(0))] + \mathbb{E}_{x,j}[w(X(t \wedge \tau(0)), I(t \wedge \tau(0)))]. \tag{22}$$

Now,

$$\begin{aligned}
&\mathbb{E}_{x,j}[w(X(t \wedge (\tau(0))), I(t \wedge \tau(0)))] \\
&\qquad = \mathbb{E}_{x,j}[w(X(t), I(t))1_{\tau(0)>t}] + \mathbb{E}_{x,j}[w(X(\tau(0)), I(\tau(0))1_{\tau(0)<t}] \\
&\qquad = \mathbb{E}_{x,j}[w(X(t), I(t))1_{\tau(0)>t}] + 0,
\end{aligned}$$

by the boundary condition in (18), the definition of $\mathbf{w}$, and the definition of $\tau(0)$. Therefore, since $\tau(0)$ is finite almost surely by Lemma 4 and $\mathbf{w}$ is bounded (since it's a continuous function on a compact set), we have that

$$\lim_{t\to\infty} \mathbb{E}_{x,j}[w(X(t \wedge (\tau(0))), I(t \wedge \tau(0)))] = 0.$$

Furthermore, by the same argument as in the proof of Theorem 3, we have that

$$\lim_{t\to\infty} \mathbb{E}_{x,j}[L(t \wedge \tau(0))] = \mathbb{E}_{x,j}[L(\tau)],$$

where we have written τ in place of $\tau(0)$ under the expectation in light of (3).

Therefore, by (22), we have that

$$v_j(x) = \rho_j w_j(x) = \rho_j \mathbb{E}_{x,j}[L(\tau)] = \mathbb{E}_x[L(\tau)1_{I(0)=j}], \quad j \in \mathcal{J}. \tag{23}$$

Summing (23) over $j \in \mathcal{J}$ and using Theorem 3 completes the proof. ∎

In the case of the simple geometry in section 4.1, we can solve this boundary value problem explicitly.

COROLLARY 7. *Let U and V_1 be as in Theorem 5. Let J be an irreducible Markov chain on $\{0,1\}$ with transition rates α and β,*

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

and thus with invariant measure $\mathbb{P}(J=0) = \rho_0 := \frac{\alpha}{\alpha+\beta}$ and $\mathbb{P}(J=1) = \rho_1 := \frac{\beta}{\alpha+\beta}$. Then, for dimension $d \in \{2,3\}$, we have that

$$\lim_{T\to\infty} \mathbb{E}[u(x,T)] = \frac{\rho_1}{\rho_0}\frac{1}{\sqrt{\alpha+\beta}} f_d(\varepsilon\sqrt{\alpha+\beta}, \delta\sqrt{\alpha+\beta}) \quad \textit{for all } x \in \overline{U\backslash V_1}, \tag{24}$$

where

$$f_2(a,b) = \frac{K_0(a)I_1(b) + I_0(a)K_1(b)}{K_1(a)I_1(b) - I_1(a)K_1(b)}, \tag{25}$$

$$\textit{and} \quad f_3(a,b) = \left[1 + \frac{1}{a} - \frac{2(1+b)}{1+b+e^{2(b-a)}(b-1)}\right]^{-1}, \tag{26}$$

where I and K are modified Bessel functions of the first and second kinds.

Remark 8. Under the assumptions of Corollary 7, it is straightforward to use (24)–(26) to check that the large time expected neurotransmitter concentration satisfies

$$\lim_{T\to\infty} \mathbb{E}[u(x,T)] \sim \frac{\rho_1}{\rho_0} g_d(\varepsilon) \quad \text{as } \varepsilon \to 0, \tag{27}$$

where g_d is given by (2). We will see in section 4.3 that the mean neurotransmitter concentration in a general domain with many nerve varicosities reduces to (27).

Proof of Corollary 7. Let $v(x) := \lim_{T\to\infty} \mathbb{E}[u(x,T)]$. By Theorem 6, we have that $v(x) = v_0(x) + v_1(x)$, where v_0 and v_1 satisfy

$$\begin{aligned} 0 &= \Delta v_0 - \beta v_0 + \alpha v_1, \\ 0 &= \Delta v_1 + \beta v_0 - \alpha v_1 \end{aligned} \tag{28}$$

with boundary conditions $\partial_\nu v_0 = \partial_\nu v_1 = 0$ at the outer boundary, $|x| = \delta$, and $v_0 = 0$, $\partial_\nu v_1 = \rho_1$ at the inner boundary, $|x| = \varepsilon$. Solving for v_0 and v_1 yields (24). ∎

4.3. Almost constant and independent of geometry and other details. In addition to the general setup of section 3.1, we further assume in this section that J is an irreducible Markov process and make one mild assumption on the asymptotic behavior of the diffusion, X, as $\varepsilon \to 0$ (see Assumption 4.1 and Remark 12). We prove that the mean neurotransmitter concentration is approximately constant in space and that this constant is independent of the geometry and other details. If we further assume that each component of J_n of J is a Markov process, then we compute this constant explicitly. Although most of the quantities in this section depend on $\varepsilon > 0$, we suppress this dependence to simplify notation.

Before giving the proof, we first give an intuitive derivation. We decompose $L(\tau)$ by conditioning on the number of visits to a neighborhood of a varicosity. To describe these visits, let $\delta > 0$ satisfy

$$\delta > \max_n \varepsilon r_n > 0, \tag{29}$$

and be sufficiently small so that each of the following sets

$$B_\delta(x_n) := \{x \in \mathbb{R}^d : |x - x_n| < \delta\}, \quad n \in \{1, \dots, N\}, \tag{30}$$

is contained in U and $B_\delta(x_n) \cap B_\delta(x_m) = \emptyset$ if $n \neq m$. Let $\sigma_{-1} = 0$ and define the sequence of stopping times, $0 \leq w_0 < \sigma_0 < w_1 < \sigma_1 < \cdots$, by

$$\begin{aligned} w_k &:= \inf\{t > \sigma_{k-1} : |X(t) - x_n| = \varepsilon r_n \text{ for some } n \in \{1, \dots, N\}\}, \\ \sigma_k &:= \inf\{t > w_k : |X(t) - x_n| = \delta \text{ for some } n \in \{1, \dots, N\}\}. \end{aligned} \tag{31}$$

Then, define L_K to be the local time that the particle accumulates during its Kth visit to a varicosity

$$L_K = L(\sigma_k \wedge \tau) - L(w_k \wedge \tau), \tag{32}$$

so that $L(\tau) = \sum_{K=0}^{\infty} L_K$.

Conditioning that the particle makes at least $K-1$ visits to a neighborhood of a varicosity and summing over K gives

$$\mathbb{E}[L(\tau)] = \sum_{K=0}^{\infty} \mathbb{P}(\tau > \sigma_{K-1}) \mathbb{E}[L_K | \tau > \sigma_{K-1}]. \tag{33}$$

Now, if the varicosities are small ($\varepsilon \ll 1$), then successive visits to varicosities are well separated in time. Hence, the states of the jump process during different visits are approximately independent. Thus,

$$\mathbb{P}(\tau > \sigma_{K-1}) \approx \big(\mathbb{P}(\tau > \sigma_0)\big)^K \quad \text{and} \quad \mathbb{E}[L_K|\tau > \sigma_{K-1}] \approx \mathbb{E}[L_0]. \tag{34}$$

By (33), we then have that

$$\mathbb{E}[L(\tau)] \approx \frac{\mathbb{E}[L_0]}{\mathbb{P}(\tau < \sigma_0)}. \tag{35}$$

Further, we can compute $\mathbb{E}[L_0]$ and $\mathbb{P}(\tau < \sigma_0)$ since they only involve the radially symmetric domain, $\{x \in U : \varepsilon r_n \le |x - x_n| \le \delta\}$ for some n. We compute these two quantities in Lemma 9 and then make this argument precise in the rest of the section. The proofs of all the lemmas are collected in the appendix.

Lemma 9. *Under the assumptions of Corollary* 7*, define the stopping times*

$$\begin{aligned} s &:= \inf\{t > 0 : |X(t)| = \delta\}, \\ \tau &:= \inf\{t > 0 : (|X(t)| = \varepsilon) \text{ and } (J_1(-t) = 0)\}. \end{aligned}$$

Define the splitting probability $p(x) = \mathbb{P}_x(\tau > s)$, and the expected local time at $|x| = \varepsilon$ before the minimum of s and τ, $h(x) = \mathbb{E}_x[L(s \wedge \tau)]$. Then, evaluating at $|x| = \varepsilon$,

$$p(x)|_{|x|=\varepsilon} = \Big(\frac{\varepsilon\eta\rho_0 \log\left(\frac{\delta}{\varepsilon}\right)\left(K_0(\delta\eta)I_1(\varepsilon\eta) + I_0(\delta\eta)K_1(\varepsilon\eta)\right)}{\rho_1(I_0(\delta\eta)K_0(\varepsilon\eta) - K_0(\delta\eta)I_0(\varepsilon\eta))} + 1\Big)^{-1} \qquad \text{if } d = 2,$$

$$p(x)|_{|x|=\varepsilon} = \frac{\delta\rho_1\left(e^{2\delta\eta} - e^{2\varepsilon\eta}\right)}{e^{2\varepsilon\eta}(\varepsilon\eta\rho_0(\delta - \varepsilon) - \delta + \varepsilon\rho_0) + e^{2\delta\eta}(\varepsilon\rho_0(\delta\eta - \varepsilon\eta - 1) + \delta)} \quad \text{if } d = 3,$$

and

$$h(x)|_{|x|=\varepsilon} = g_d(\varepsilon, \delta)p(x)|_{|x|=\varepsilon},$$

where

$$g_d(\varepsilon, \delta) = \begin{cases} \varepsilon \log(\delta/\varepsilon) & \text{if } d = 2, \\ \varepsilon(\delta - \varepsilon)/\delta & \text{if } d = 3. \end{cases}$$

Remark 10. Under the assumptions of Lemma 9, it is straightforward to check that $\lim_{\varepsilon \to 0} p(x)|_{|x|=\varepsilon} = \rho_1$ and

$$\frac{h(x)|_{|x|=\varepsilon}}{1 - p(x)|_{|x|=\varepsilon}} \sim \frac{\rho_1}{\rho_0} g_d(\varepsilon) \sim \lim_{T\to\infty} \mathbb{E}[u(x, T)] \quad \text{as } \varepsilon \to 0,$$

where g_d is given by (2).

Before stating and proving a precise version of (35), we need a few lemmas. The first lemma checks that the first passage time of X to a varicosity diverges as the varicosity radius ε shrinks to zero.

Lemma 11. *Recall w_0 in* (31)*. If $x \in U\backslash\{x_1, \dots, x_N\}$, then for each $T > 0$*

$$\mathbb{P}_x(w_0 < T) \to 0 \quad \text{as } \varepsilon \to 0.$$

We now make the following mild assumption.

ASSUMPTION 4.1. *If $x \in U \backslash \{x_1, \dots, x_N\}$ and $n \in \{1, \dots, N\}$, then*

$$\mathbb{P}_x(X(w_0) \in \partial V_n) \to \pi_n := \frac{r_n}{\sum_{m=1}^N r_m} \quad \text{as } \varepsilon \to 0.$$

Remark 12. Assumption 4.1 is very mild. In $d = 3$, it has been shown to hold using formal asymptotic PDE analysis [15] (see also [34]). Similar analysis has shown it holds in $d = 2$ if $r_n = r$ for all n [14]. Furthermore, if each varicosity has the same radius and each component J_n of J is itself a Markov process with the same invariant measure, then the assumption is superfluous.

For notational ease, we let $I(t) = J(-t)$ denote the time reversal of J. We also use $\mathbb{P}_{x,i}$ and $\mathbb{E}_{x,i}$ to denote probability or expectation conditioned on $X(0) = x$ and $I(0)$ in state $i \in \mathcal{J}$. Our next lemma below asserts that no matter where $(X(0), I(0))$ starts, its distribution at the first time X hits a varicosity is approximately the product measure $\pi \times \rho$.

LEMMA 13. *Let $\eta > 0$ and $x \in U \backslash \{x_1, \dots, x_N\}$. Then there exists an $\varepsilon_0 = \varepsilon_0(\eta, x) > 0$ such that if $\varepsilon < \varepsilon_0$, then*

$$|\mathbb{P}_{x,j}(X(w_0) \in \partial V_n \cap I(w_0) = i) - \pi_n \rho_i| < \eta$$

for all $i, j \in \mathcal{J}$ and $n \in \{1, \dots, N\}$.

Our next lemma extends Lemma 13 to the kth time X hits a varicosity.

LEMMA 14. *Let $0 \le w_0 < \sigma_0 < w_1 < \sigma_1 < \cdots$ be* (31). *For $k \in \mathbb{N} \cup \{0\}$, $i \in \mathcal{J}$, and $n \in \{1, \dots, N\}$, let $A_{n,i}^k$ denote the event*

$$A_{n,i}^k := \{X(w_k) \in \partial V_n \cap I(w_k) = i\}. \tag{36}$$

Let $\eta > 0$ and $x \in U \backslash \{x_1, \dots, x_N\}$. Then there exists an $\varepsilon_1 = \varepsilon_1(\eta, \delta, x)$ such that if $\varepsilon < \varepsilon_1$ and $B \in \mathcal{F}(\sigma_{k-1})$, where $\mathcal{F}(\sigma_{k-1})$ is the σ-algebra generated by $\{(X(t), J(t))\}_{t=0}^{\sigma_{k-1}}$, then

$$|\mathbb{P}_x(A_{n,i}^k | B) - \pi_n \rho_i| < \eta$$

for all $k \in \mathbb{N} \cup \{0\}$, $i \in \mathcal{J}$, and $n \in \{1, \dots, N\}$.

With these lemmas in place, we are ready to prove that if the nerve varicosities are small, then the mean neurotransmitter is approximately constant in space and that this constant does not depend on many details in the problem.

THEOREM 15. *Assume the setup of section* 3.1, *suppose Assumption* 4.1 *holds, and assume J is an irreducible Markov process. Then there exists a constant, $\kappa = \kappa\big(d, \{J_n\}_{n=1}^N, \varepsilon \boldsymbol{r}\big)$, depending only on the spatial dimension, $d \in \{2, 3\}$, the marginal statistics of each of the N components, $\{J_n\}_{n=1}^N$, of the jump process J, and the radii of the varicosities, $\varepsilon \boldsymbol{r} = \varepsilon(r_1, \dots, r_N)$, so that for each $x \in \overline{U} \backslash \{x_1, \dots, x_N\}$, we have*

$$\lim_{t \to \infty} \mathbb{E}[u(x,t)] \sim \kappa \quad \text{as } \varepsilon \to 0.$$

Remark 16. We note that the constant, κ, is independent of correlations between different nerve varicosities. That is, κ is unchanged if the varicosities fire synchronously, independently, or with some nontrivial correlation.

We will see in the proof that if each J_n is a Markov process with invariant measure, $\mathbb{P}(J_n(0)=0)=\rho_0^{(n)}$ and $\mathbb{P}(J_n(0)=1)=\rho_1^{(n)}$, then using Remark 10 we have

$$\kappa(d,\rho,\varepsilon\mathbf{r})=\frac{\sum_{n=1}^N \rho_1^{(n)} r_n g_d(\varepsilon r_n)}{\sum_{n=1}^N \rho_0^{(n)} r_n},$$

where g_d is given by (2).

Remark 17. Our proof of Theorem 15 can be viewed as a probabilistic version of PDE matched asymptotics. In such PDE analysis, one typically constructs an outer solution that is valid in the bulk of the domain and an inner solution that is valid only in a neighborhood of the boundary [15, 16, 27, 36]. Matching these two solutions then gives a global solution. Analogously, our proof computes outer statistics of a Brownian particle that are valid when the particle is far from a boundary and inner statistics that are valid when the particle is near a boundary. Conditioning on the number of times the particle is in a neighborhood of the boundary then gives global statistics. We note that we employed similar ideas in our analysis of mean first passage times in random environments in [7, 8].

Proof of Theorem 15. For each n we claim that $\mathbb{P}_x(\tau>\sigma_0)=\mathbb{P}_y(\tau>\sigma_0)$ and $\mathbb{E}_x[L_0]=\mathbb{E}_y[L_0]$ for all $x,y\in\partial V_n$ by symmetry. To see this, recall from (30)–(31) that $\sigma_0\geq 0$ is the first time that $X(t)$ leaves the ball $B_\delta(x_n)$, where $\delta>\max_n \varepsilon r_n>0$ is sufficiently small so that $B_\delta(x_n)\subset U$ and $B_\delta(x_n)\cap B_\delta(x_m)=\emptyset$ if $n\neq m$. Hence, if $x,y\in\partial V_n$, then the problem is radially symmetric for $t\in[0,\sigma_0]$. The event $\{\tau>\sigma_0\}$ and the random variable L_0 are measurable with respect to $\mathcal{F}(\sigma_0)$, and thus the claim is verified.

Therefore if $x\in\partial V_n$, let $\mathbb{P}_n(\tau>\sigma_0)$ and $\mathbb{E}_n[L_0]$ denote $\mathbb{P}_x(\tau>\sigma_0)$ and $\mathbb{E}_x[L_0]$, respectively. Similarly, if $x\in\partial V_n$, let $\mathbb{P}_{n,i}(\tau>\sigma_0)$ and $\mathbb{E}_{n,i}[L_0]$ denote $\mathbb{P}_{x,i}(\tau>\sigma_0)$ and $\mathbb{E}_{x,i}[L_0]$, respectively. Define

$$p:=\sum_{n=1}^N \mathbb{P}_n(\tau>\sigma_0)\pi_n \quad\text{and}\quad l:=\sum_{n=1}^N \mathbb{E}_n[L_0]\pi_n$$

and $\kappa=l/(1-p)$. Suppressing the x-dependence, define $l_K=l_K(x)$ for $K\geq 0$ by

$$l_K:=\frac{\mathbb{E}_x[L_K 1_{\{\tau>\sigma_{K-1}\}}]}{\mathbb{P}_x(\tau>\sigma_{K-1})}=\frac{\mathbb{E}_x[L_K]}{\mathbb{P}_x(\tau>\sigma_{K-1})}, \tag{37}$$

where L_K and σ_{K-1} are as in (32) and (31). In light of Theorem 3, we need to show that the following quantity tends to zero as $\varepsilon\to 0$:

$$\begin{aligned}\Big|\frac{l/(1-p)}{\mathbb{E}_x[L(\tau)]}-1\Big| &= \frac{1}{\mathbb{E}_x[L(\tau)]}\left|\sum_{K=0}^\infty \mathbb{E}_x[L_K]-l\sum_{K=0}^\infty p^K\right| \\ &\leq \frac{1}{\mathbb{E}_x[L(\tau)]}\left|\sum_{K=0}^\infty \mathbb{P}_x(\tau>\sigma_{K-1})l_K-l\sum_{K=0}^\infty p^K\right| \\ &\leq \frac{1}{\mathbb{E}_x[L(\tau)]}\sum_{K=0}^\infty \Big(\big|\mathbb{P}_x(\tau>\sigma_{K-1})-p^K\big|l_K+p^K\big|l_K-l\big|\Big).\end{aligned} \tag{38}$$

We work on $|l_K-l|$ first. Let $A_{n,i}^K$ be as in (36) and define

$$\tilde{L}_K:=L(\sigma_K\wedge\tau_K)-L(w_K),$$

where τ_K is the stopping time

$$\tau_K = \inf\{t > w_K : (X(t) \in \partial V_n) \text{ and } (I_n(t) = 0) \text{ for some } n \in \{1, \dots, N\}\}. \tag{39}$$

Then $L_K = 1_{\{\tau > \sigma_{K-1}\}} L_K = 1_{\{\tau > \sigma_{K-1}\}} \tilde{L}_K$ almost surely and thus using the tower property of conditional expectation we have that

$$\mathbb{E}_x[L_K] = \mathbb{E}_x[1_{\{\tau > \sigma_{K-1}\}} \tilde{L}_K] = \mathbb{E}_x[1_{\{\tau > \sigma_{K-1}\}} \mathbb{E}_x[\tilde{L}_K | \mathcal{F}(w_K)]],$$

where $\mathcal{F}(w_k)$ is the σ-algebra generated by $\{(X(t), I(t))\}_{t=0}^{w_k}$. By the strong Markov property we have that

$$\mathbb{E}_x[\tilde{L}_K | \mathcal{F}(w_K)] = \mathbb{E}_{X(w_K), I(w_K)}[L_0].$$

Thus,

$$\mathbb{E}_x[L_K] = \sum_{n,i} \mathbb{E}_x[1_{\{\tau > \sigma_{K-1}\}} 1_{A_{n,i}^K} \mathbb{E}_{n,i}[L_0]] = \sum_{n,i} \mathbb{E}_{n,i}[L_0] \mathbb{P}_x(\tau > \sigma_{K-1} \cap A_{n,i}^K). \tag{40}$$

Combining (37) and (40), we have that

$$l_K = \sum_{n,i} \mathbb{E}_{n,i}[L_0] \mathbb{P}_x(A_{n,i}^K | \tau > \sigma_{K-1}).$$

Let $\eta > 0$. By Lemma 14, there exists an $\varepsilon_1 > 0$ such that if $\varepsilon < \varepsilon_1$, then

$$|\mathbb{P}_x(A_{n,i}^K | \tau > \sigma_{K-1}) - \pi_n \rho_i| < \eta \quad \text{for all } n, i, K.$$

Now, $\mathbb{E}_x[L(\tau)] \geq \mathbb{E}_x[L_0]$ and thus for $\varepsilon < \varepsilon_1$ we have that

$$\begin{aligned}\frac{|l_K - l|}{\mathbb{E}_x[L(\tau)]} &\leq \eta \frac{\sum_{n,i} \mathbb{E}_{n,i}[L_0]}{\sum_{n,i} \mathbb{E}_{n,i}[L_0] \rho_i \mathbb{P}_x(X(w_0) \in \partial V_n)} \\ &\leq \frac{\eta}{\left(\min_{i \in \mathcal{J}} \rho_i\right)\left(\min_{n \in \{1,\dots,N\}} \mathbb{P}_x(X(w_0) \in \partial V_n)\right)}\end{aligned}$$

for all K. By Assumption 4.1, there exists a constant C independent of ε and x such that

$$\left(\min_{i \in \mathcal{J}} \rho_i\right) \left(\min_{n \in \{1,\dots,N\}} \mathbb{P}_x(X(w_0) \in \partial V_n)\right) > C > 0,$$

and thus for $\varepsilon < \varepsilon_1$,

$$\frac{|l_K - l|}{\mathbb{E}_x[L(\tau)]} \leq \frac{\eta}{C} \quad \text{for all } K. \tag{41}$$

We now work on $|\mathbb{P}_x(\tau > \sigma_{K-1}) - p^K|$. Recall (39) and define the event $B_k := \{\tau_k \notin [w_k, \sigma_k)\}$. Then

$$\mathbb{P}_x(\tau > \sigma_{K-1}) = \mathbb{P}_x(\cap_{k=0}^{K-1} B_k) = \prod_{k=0}^{K-1} \mathbb{P}_x(B_k | \cap_{j=0}^{k-1} B_j).$$

Observe that by the tower property of conditional expectation and the strong Markov property, we have that

$$\begin{aligned}\mathbb{P}_x(B_k|\cap_{j=0}^{k-1}B_j) &= \frac{1}{\mathbb{P}_x(\cap_{j=0}^{k-1}B_j)}\mathbb{E}_x[1_{\{\cap_{j=0}^{k-1}B_j\}}\mathbb{E}_x[1_{B_k}|\mathcal{F}(w_k)]] \\ &= \frac{1}{\mathbb{P}_x(\cap_{j=0}^{k-1}B_j)}\mathbb{E}_x[1_{\{\cap_{j=0}^{k-1}B_j\}}\mathbb{P}_{X(w_k),I(w_k)}(\tau>\sigma_0)].\end{aligned}$$

Hence,

$$\begin{aligned}\mathbb{P}_x(B_k|\cap_{j=0}^{k-1}B_j) &= \frac{1}{\mathbb{P}_x(\cap_{j=0}^{k-1}B_j)}\sum_{n,i}\mathbb{E}_x[1_{\{\cap_{j=0}^{k-1}B_j\}}1_{A_{n,i}^k}\mathbb{P}_{X(w_k),I(w_k)}(\tau>\sigma_0)] \\ &= \sum_{n,i}\mathbb{P}_x(A_{n,i}^k|\cap_{j=0}^{k-1}B_j)\mathbb{P}_{n,i}(\tau>\sigma_0).\end{aligned}$$

Therefore, by Lemma 14 there exists an $\varepsilon_2>0$ such that if $\varepsilon<\varepsilon_2$, then for all k

$$|\mathbb{P}_x(B_k|\cap_{j=0}^{k-1}B_j)|-p|\leq\sum_{n,i}\mathbb{P}_{n,i}(\tau>\sigma_0)\big|\mathbb{P}_x(A_{n,i}^k|\cap_{j=0}^{k-1}B_j)-\pi_n\rho_i\big|\leq\eta.$$

Therefore for all K

(42)

$$\begin{aligned}|\mathbb{P}_x(\tau>\sigma_{K-1})-p^K| &= \left|\prod_{k=0}^{K-1}\mathbb{P}_x(B_k|\cap_{j=0}^{k-1}B_j)-p^K\right| \\ &\leq\sum_{m=0}^{K-1}\big|\mathbb{P}_x(B_m|\cap_{j=0}^{m-1}B_j)-p\big|p^{K-m-1}\prod_{k=0}^{m-1}\mathbb{P}_x(B_k|\cap_{j=0}^{k-1}B_j) \\ &\leq\sum_{m=0}^{K-1}\eta(p+\eta)^{K-1}=\eta K(p+\eta)^{K-1}.\end{aligned}$$

Furthermore, by (41) we have that if $\varepsilon<\varepsilon_1$, then for all K

$$\frac{l_K}{\mathbb{E}_x[L(\tau)]}\leq\frac{|l_K-l|}{\mathbb{E}_x[L(\tau)]}+\frac{l}{\mathbb{E}_x[L(\tau)]}\leq\frac{\eta}{C}+\frac{l}{\mathbb{E}_x[L(\tau)]}. \tag{43}$$

By Assumption 4.1, there exists an $\varepsilon_3>0$ such that if $\varepsilon<\varepsilon_3$, then for all n

$$|\mathbb{P}_x(X(w_0)\in\partial V_n)-\pi_n|<\frac{\pi_n}{2},$$

since $\pi_n>0$ for all n. Thus,

$$\frac{l}{\mathbb{E}_x[L(\tau)]}\leq\frac{\sum_{n,i}\mathbb{E}_{n,i}[L_0]\pi_n\rho_i}{\sum_{n,i}\mathbb{E}_{n,i}[L_0]\mathbb{P}_x(X(w_0)\in\partial V_n)\rho_i}\leq 2. \tag{44}$$

Combining (38) with (41), (42), (43), and (44), we have that if $\varepsilon<\min\{\varepsilon_1,\varepsilon_2,\varepsilon_3\}$, then

$$\frac{1}{\mathbb{E}_x[L(\tau)]}\Big|\mathbb{E}_x[L(\tau)]-\frac{l}{1-p}\Big|\leq\sum_{K=0}^{\infty}\bigg(\Big(\frac{\eta}{C}+2\Big)\eta K(p+\eta)^{K-1}+\frac{\eta}{C}p^K\bigg).$$

Since $\eta>0$ was arbitrary and since C is independent of ε, it remains only to check that $p\in(0,1)$ is bounded away from 1 as a function of ε. This is immediate since $\mathbb{P}_{n,i}(\tau>\sigma_0)=0$ if state $i\in\mathcal{J}$ corresponds to $I_n(t)=0$. $\square$

5. Discussion. We have formulated and analyzed a mathematical model of the fundamental neural mechanism known as volume transmission. Our model consists of a PDE in a bounded two- or three-dimensional domain with randomly switching boundary conditions at interior holes. Representing the solution to this random PDE by a certain expected local time in a random environment, we then investigated the mean solution to the PDE in the limit of small interior holes.

This limit corresponds to nerve varicosities being much smaller than the distance between varicosities. The distance between varicosities varies, but for serotonin there are about 2.6×10^6 varicosities per cubic millimeter [41] or a distance of about $l = 7\,\mu$m between varicosities. In Figure 1 of [35], varicosities are typically separated by about $l = 20\,\mu$m. The mean radius of varicosities in [41] is $R = .3\,\mu$m. Hence, $\varepsilon = R/l$ is much less than 1,

$$.015 = .3/20 \leq \varepsilon \leq .3/7 \approx .04.$$

Furthermore, in Lemma 13 we took ε sufficiently small to ensure that the Markov process controlling firing equilibrates by the time a diffusing particle hits a varicosity. The dimensionless constant characterizing this equilibration time is

$$\frac{D}{l^2}\frac{1}{\alpha+\beta},$$

where D is the neurotransmitter diffusion coefficient and α, β are the rates at which a neuron goes from firing to quiescent and from quiescent to firing. Reasonable values are $D = 100\,\frac{\mu\mathrm{m}^2}{\mathrm{sec}}$, $\alpha = 200\,\frac{1}{\mathrm{sec}}$, and $\beta = 1\,\frac{1}{\mathrm{sec}}$ [24], making the dimensionless equilibration time no larger than .01. Since the time to find a varicosity is on the order of $1/\varepsilon$ in dimension three [15] and $-\log\varepsilon$ in dimension two [16], this requirement of Lemma 13 is likely satisfied by real neural systems.

Naturally, our model neglects some important biological details. For example, the neurotransmitter release rate is almost certainly not constant while a neuron is firing, nor are the varicosities perfectly absorbing when a neuron is quiescent. Furthermore, we have ignored the presence of other types of cells in the volume which may absorb neurotransmitter or hinder its diffusion. These limitations notwithstanding, we have discovered the surprising result that the neurotransmitter concentration is approximately constant across the extracellular space and that this constant is independent of the number and arrangement of nerve varicosities, the geometry and size of the extracellular space, and any firing correlations between neurons. A forthcoming paper will explore the biological implications of these results.

We note that our calculations give only the leading order approximation to the expected neurotransmitter concentration. To calculate the expected neurotransmitter concentration exactly, one must solve the PDE boundary value problem that we derived in Theorem 6. In future work, we will use matched asymptotic analysis to approximate higher order terms to the solution of this PDE boundary value problem and compare it to detailed numerical simulations.

Finally, while we used the local time representation of Theorem 1 to study the mean neurotransmitter concentration, one can also use this representation to study other neurotransmitter statistics. Most generally, one can use Theorem 1 to investigate M-point correlations in space and time. As a specific and biologically relevant example, Theorem 1 yields that the variance of neurotransmitter has the representation

$$\mathrm{Var}(u(x,T)) = \mathrm{Var}\big(\mathbb{E}_x[L(\tau(T)\wedge T)|J]\big). \tag{45}$$

Using an argument similar to the one in Lemma 4 and Theorem 3, one can take $T \to \infty$ in (45) and obtain

$$\lim_{T\to\infty} \mathrm{Var}(u(x,T)) = \mathrm{Var}\big(\mathbb{E}_x[L(\tau)|J]\big) = \mathbb{E}\big[\big(\mathbb{E}_x[L(\tau)|J] - \mathbb{E}_x[L(\tau)]\big)^2\big]. \tag{46}$$

Equation (46) says that the large time variance of the solution to the random PDE is how much the expected local time varies over different realizations of the jump process, J. This leads us to conjecture that the variance of neurotransmitter is small in the majority of the extracellular space and spikes near each varicosity. To see this, observe that if $x \in E$ is near a nerve varicosity, then a Brownian particle starting at x will (with high probability) hit that varicosity almost immediately. Thus, $\mathbb{E}_x[L(\tau)|J]$ will be very different depending if the jump process is 0 or 1 at early times. On the other hand, $\mathbb{E}_x[L(\tau)|J]$ will depend only weakly on the particular realization of J if x is far from a varicosity, since in such a case the distribution of hitting times to varicosities will be very flat.

Furthermore, if the varicosities are small, then the distribution of hitting times to varicosities will necessarily be very flat outside a vanishingly small neighborhood of each varicosity. Therefore, one expects that

$$\mathbb{E}_x[L(\tau)|J] \approx \mathbb{E}_x[L(\tau)] \quad \text{if } \varepsilon \ll 1. \tag{47}$$

In words, (47) says that knowing the realization of J doesn't help you predict the local time because you don't know when the particle will hit a varicosity if the varicosities are small. Making this precise, we make the following conjecture.

Conjecture 18. *The coefficient of variation of $u(x,T)$ at large time vanishes in the small varicosity limit. That is, if $x \in U \backslash \{x_1, \dots, x_N\}$, then*

$$\lim_{T\to\infty} \frac{\sqrt{\mathrm{Var}(u(x,T))}}{\mathbb{E}[u(x,T)]} \to 0, \quad \text{as } \varepsilon \to 0.$$

This conjecture will be investigated using numerical simulation in a future paper.

Appendix A. In this appendix, we prove all of our lemmas.

Proof of Lemma 4. Let n^* be such that $\mathbb{P}(J_{n^*}(t) = 0) > 0$. Define

$$s := \inf\{t > 0 : X(t) \in \partial V_{n^*}\}.$$

It is a standard result on mean first passage times of Brownian motion [37] that

$$\gamma := \sup_{x \in \overline{E}} \mathbb{E}_x[s] < \infty.$$

Let $\sigma > 0$ and $q \in (0,1)$ be as in (4), and define the sequence of stopping times, $\{s_k\}_{k=0}^{\infty}$, by $s_0 = 0$, and

$$s_k = \inf\{t > s_{k-1} + \sigma : X(t) \in \partial V_{n^*}\} \quad \text{for } k \geq 1.$$

Observe that

$$s_k - s_{k-1} > \sigma \quad \text{almost surely for all } k \in \mathbb{N}, \tag{48}$$

and

$$\sup_{x \in \overline{E}} \mathbb{E}_x[s_k] \leq k(\gamma + \sigma) \quad \text{for all } k \in \mathbb{N}. \tag{49}$$

Define the sequence of events, $\{A_k\}_{k=1}^{\infty}$, by

$$A_k = \left\{ \bigcap_{j=1}^{k-1} \{J_{n^*}(-s_j) = 1\} \right\} \cap \{J_{n^*}(-s_k) = 0\}.$$

Then the sample space is the disjoint union,

$$\Omega = \left\{ \bigcup_{k=1}^{\infty} A_k \right\} \cup A_\infty, \quad \text{where} \quad A_\infty = \bigcap_{j=1}^{\infty} \{J_{n^*}(-s_j) = 1\}.$$

By (4) and (48), we have that $\mathbb{P}(A_\infty) \leq q^k$ for all $k \in \mathbb{N}$ and thus $\mathbb{P}(A_\infty) = 0$. By the tower property of conditional expectation, conditioning over realizations of the particle X and using (49) yield

$$\mathbb{E}_x[s_k 1_{A_k}] = \mathbb{E}_x[s_k \mathbb{E}_x[1_{A_k}|X]] \leq q^{k-1}\mathbb{E}_x[s_k] \leq q^{k-1}k(\gamma+\sigma),$$

since $\mathbb{E}_x[1_{A_k}|X] \leq q^{k-1}$ almost surely by (4). Therefore,

$$\sup_{x\in\overline{E}} \mathbb{E}_x[\tau] \leq \sum_{k=1}^{\infty} \sup_{x\in\overline{E}} \mathbb{E}_x[s_k 1_{A_k}] \leq (\gamma+\sigma)\sum_{k=1}^{\infty} kq^{k-1} < \infty. \qquad \square$$

Proof of Lemma 9. Using an argument that is very similar to the proof of Theorem 6, one can show that $p(x) = p_0(x) + p_1(x)$, where p_0 and p_1 satisfy (28) with boundary conditions $p_0 = \frac{\alpha}{\alpha+\beta}$, $p_1 = \frac{\beta}{\alpha+\beta}$ at the outer boundary, $|x| = \delta$, and $\partial_\nu p_1 = p_0 = 0$ at the inner boundary, $|x| = \varepsilon$. Solving these exactly yields $p(x)$.

Similarly, $h(x) = h_0(x) + h_1(x)$, where h_0 and h_1 satisfy (28) with boundary conditions $h_0 = 0$, $h_1 = 0$ at the outer boundary, $|x| = \delta$, and $h_0 = 0$, $\partial_\nu h_1 = \frac{\beta}{\alpha+\beta}$ at the inner boundary, $|x| = \varepsilon$. Solving these exactly yields $h(x)$. $\square$

Proof of Lemma 11. For each $m \geq 1$, let A_m be the event that $w_0 < T$ for $\varepsilon = 1/m$. Since $A_{m+1} \subset A_m$ for $m \geq 1$, it follows that $\mathbb{P}_x(A_m) \to \mathbb{P}_x(\cap_k A_k)$ as $m \to \infty$. However, $\mathbb{P}_x(\cap_k A_k) = 0$ since Brownian motion in dimension $d \geq 2$ almost surely does not hit a given finite set of points, assuming it does not start at one of those points. $\square$

Proof of Lemma 13. Since J is an irreducible Markov process with unique invariant distribution $\rho \in \mathbb{R}^{|\mathcal{J}|}$, it follows that the time reversal of J is also an irreducible Markov process with unique invariant distribution $\rho \in \mathbb{R}^{|\mathcal{J}|}$ (see, for example, section 3.7 in [32]) and thus there exists a $T = T(\eta) > 0$ so that

$$|\mathbb{P}_{x,j}(I(t) = i) - \rho_i| < \eta \quad \text{for all } t > T,\ x \in \overline{E}, \text{ and } i, j \in \mathcal{J}.$$

Further, by Lemma 11, there exists an $\varepsilon_1 = \varepsilon_1(T)$ so that

$$\mathbb{P}_x(w_0 < T) < \eta \text{ for all } \varepsilon < \varepsilon_1. \tag{50}$$

By Assumption 4.1, there exists an $\varepsilon_2 = \varepsilon_2(x)$ so that

$$|\mathbb{P}_{x,j}(X(w_0) \in \partial V_n) - \pi_n| < \eta \quad \text{for all } \varepsilon < \varepsilon_2,\ j \in \mathcal{J}, \text{ and } n \in \{1, \dots, N\}.$$

Let $\varepsilon < \varepsilon_0 := \min\{\varepsilon_1, \varepsilon_2\}$. Then, by (50) and the tower property of conditional expectation, we have that

$$\begin{aligned}\mathbb{P}_{x,j}(X(w_0) \in \partial V_n \cap I(w_0) = i) &\leq \mathbb{E}_{x,j}[1_{\{X(w_0)\in\partial V_n\}} 1_{\{w_0 > T\}} 1_{\{I(w_0)=i\}}] + \eta \\ &= \mathbb{E}_{x,j}[1_{\{X(w_0)\in\partial V_n\}} 1_{\{w_0 > T\}} \mathbb{E}_{x,j}[1_{\{I(w_0)=i\}}|\mathcal{F}_{w_0}^X]] + \eta,\end{aligned}$$

where $\mathcal{F}^X_{w_0}$ denotes the σ-algebra generated by X until it hits a varicosity, $\mathcal{F}^X_{w_0} = \sigma(\{X(t)\}_{t=0}^{w_0})$. Therefore, adding and subtracting $\mathbb{E}_{x,j}[1_{\{X(w_0)\in\partial V_n\}}1_{\{w_0>T\}}\rho_i]$ yields

$$\begin{aligned}
&|\mathbb{P}_{x,j}(X(w_0)\in\partial V_n \cap I(w_0)=i) - \pi_n\rho_i| \\
boig \qquad &\leq \mathbb{E}_{x,j}\Big[1_{\{X(w_0)\in\partial V_n\}}1_{\{w_0>T\}}\big|\mathbb{E}_{x,j}[1_{\{I(w_0)=i\}}|\mathcal{F}^X_{w_0}] - \rho_i\big|\Big] \\
&\quad + \big|\mathbb{P}_{x,j}(X(w_0)\in\partial V_n) - \pi_n\big|\rho_i + 2\eta.
\end{aligned}$$

By the choice of T,

$$1_{\{w_0>T\}}\big|\mathbb{E}_{x,j}[1_{\{I(w_0)=i\}}|\mathcal{F}^X_{w_0}] - \rho_i\big| < \eta \quad \text{almost surely,}$$

and by the choice of ε

$$\big|\mathbb{P}_{x,j}(X(w_0)\in\partial V_n) - \pi_n\big| < \eta,$$

so the proof is complete. ∎

Proof of Lemma 14. By the tower property of conditional expectation and the strong Markov property, we have that

$$\begin{aligned}
\mathbb{P}_x(A^k_{n,i}|B) &= \frac{1}{\mathbb{P}_x(B)}\mathbb{E}_x[1_{A^k_{n,i}}1_B] = \frac{1}{\mathbb{P}_x(B)}\mathbb{E}_x[1_B\mathbb{E}_x[1_{A^k_{n,i}}|\mathcal{F}(\sigma_{k-1})]] \\
&= \frac{1}{\mathbb{P}_x(B)}\mathbb{E}_x[1_B\mathbb{P}_{X(\sigma_{k-1}),I(\sigma_{k-1})}(A^0_{n,i})].
\end{aligned}$$

Now, $X(\sigma_{k-1}) \in \cup_{n=1}^N \partial B_\delta(x_n) =: S$ almost surely, where $B_\delta(y)$ is as in (30). This set, S, is compact so if $\varepsilon_0(\eta, y)$ is as in Lemma 13, then $\varepsilon_0(\eta, y)$ must achieve its infimum for $y \in S$. Thus $\varepsilon_1 := \inf_{y\in S}\varepsilon_0(\eta, y) > 0$. Therefore, if $\varepsilon < \varepsilon_1$, Lemma 13 ensures that

$$|\mathbb{P}_{X(\sigma_{k-1}),I(\sigma_{k-1})}(A^0_{n,i}) - \pi_n\rho_i| < \eta \quad \text{almost surely,}$$

and the proof is complete. ∎

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