Trapping in and escape from branched structures of neuronal dendrites

Robin Jose, Ludger Santen, and M. Reza Shaebani

Department of Theoretical Physics & Center for Biophysics, Saarland University, 66123 Saarbrücken, Germany

ABSTRACT We present a coarse-grained model for stochastic transport of noninteracting chemical signals inside neuronal dendrites and show how first-passage properties depend on the key structural factors affected by neurodegenerative disorders or aging: the extent of the tree, the topological bias induced by segmental decrease of dendrite diameter, and the trapping probabilities in biochemical cages and growth cones. We derive an exact expression for the distribution of first-passage times, which follows a universal exponential decay in the long-time limit. The asymptotic mean first-passage time exhibits a crossover from power-law to exponential scaling upon reducing the topological bias. We calibrate the coarse-grained model parameters and obtain the variation range of the mean first-passage time when the geometrical characteristics of the dendritic structure evolve during the course of aging or neurodegenerative disease progression (A few disorders are chosen and studied for which clear trends for the pathological changes of dendritic structure have been reported in the literature). We prove the validity of our analytical approach under realistic fluctuations of structural parameters, by comparing to the results of Monte Carlo simulations. Moreover, by constructing local structural irregularities, we analyze the resulting influence on transport of chemical signals and formation of heterogeneous density patterns. Since neural functions rely on chemical signal transmission to a large extent, our results open the possibility to establish a direct link between the disease progression and neural functions.

INTRODUCTION

The complex behavior of advanced nervous systems mainly originates from the elaborate structure of neuronal dendrites [1]. The functions of the nervous system substantially rely on the diffusion of chemical signals, which is strongly affected by the dendrite structure. The branching morphology of dendrites allows the neurons to control the transmission time of signals and construct a complex network of signaling pathways. While dendritic trees share some structural features, e.g. branching at acute angles or decreasing in their diameter when moving distally from soma, their morphology varies widely in different neuronal types and regions, reflecting their diverse functions [2]. Moreover, the presence of small protrusions along dendrites, called spines, adds to the complexity of the system. Spines receive excitatory synaptic inputs, temporarily compartmentalize them, and undergo dynamic structural changes regulated by neuronal activity [3]. Bidirectional communication between the spines and the soma (via e.g. Ca$^{2+}$, soluble intracellular domains, and subunits of the nuclear import machinery) is critical for long-term plasticity, neuronal development, and information processing capabilities [4]. Additionally, synaptic activation can trigger signaling pathways which spread locally in the dendritic channel and influence neighboring synapses [5].

Understanding how signal transmission is governed by the structure is becoming more important, because pervasive changes of dendritic structure have been reported due to aging [6–8] or neurodegenerative disorders [9–10], such as Alzheimer’s disease [11–13], (i) the population and spatial extent of branches [8, 11], (ii) the thickness, length, and even curvature of dendritic channels [6, 9, 11], or (iii) the density, shape, and spatial distribution of spines [6–13] can be affected. To establish a link between the structural changes and subsequent alterations of neural functions, a deep understanding of the role of structure on transport of ions or molecules is still lacking. The attempts have been mainly limited to the determination of the impact of spine shape on diffusional and first-passage properties of signals inside spines [14–21]. The role of spine density has also been studied by considering comb-like structures or (periodically) distributed traps along a channel [22–24]. However, the precise estimation of escape time from dendritic trees to reach soma is a difficult task. The complication arises due to complex branching morphology, presence of spines along the tree, irregular shape of junctions, and varying cross-section radius of dendritic channels.

Here we propose a coarse-grained approach to map the stochastic transport of ions and molecules inside neuronal dendrites to an effective one-dimensional random walk of noninteracting particles in a confined geometry. Coarse-grained random walk models have been previously employed to successfully describe the influence of topological and geometrical characteristics of the structure on diffusion in labyrinthine environments (see e.g. [25] for oxygen absorption in the human lung). Our effective 1D random walk model enables us to obtain insightful analytical results for mean first-passage times (MFPTs) in complex structures of neuronal dendrites. Various types of 1D random walks have been previously studied, including biased [26–31] and persistent [29–32] walks as well as the walks with absorption along the path [28] or at the boundaries [33–35]. Here, in view of the morphological differences between the dendrites of healthy and degenerate brain tissues, we concentrate on
the major characteristics affected by neurodegenerative diseases: the overall extent of dendritic trees, the thicknesses of channels, and the structure and density of spines. By combining appropriate boundary conditions at the two ends of a finite one-dimensional system, partial absorption along the path, and biased motion in an effective 1D random walk model, we construct a suitable framework to study signal transmission in dendrites. We disentangle the contributions of key structural features to first-passage properties and verify that the scaling behavior of the asymptotic MFPT changes below a threshold value of the topological bias induced by hierarchical reduction of branch diameter. We evaluate the variation range of the mean time required for chemical signals to travel from the synapses to the soma in the course of some specific neurodegenerative disease progression. Moreover, the applicability of our theoretical approach to realistic dendritic structures with spatial heterogeneities is addressed and the role of local structural changes on signal transmission and formation of heterogeneous density patterns is discussed.

**METHODS**

By adopting a mesoscopic perspective for transmission of ions and molecules inside dendrites, we consider the motion of a noninteracting random walker on the nodes of a tree-like regular network with a finite depth \( d \), parameterizing the extent of branches [Fig. 1(b)]. Each node is identified by its depth \( n \), ranging from 0 (soma) to \( d \) (dead ends). After entering the network, the walker randomly jumps to the neighboring nodes until it is absorbed in the target, i.e., soma. To take into account the stochastic trapping events in spines, we assume that the walker either moves in the channel or resides inside biochemical cages with probabilities \( q \) or \( 1-q \), respectively. This way we map the problem to a stochastic two-state model. Such models have been widely employed to describe altering phases of motion in biological systems [34].

![Illustration of the model. An example tree structure with \( d=5 \) and \( p=0.5 \) is shown. The arrows indicate possible choices at junctions or dead ends, described by Eqs. (1). As a visual guide, the ratio between the diameters of parent and child branches is taken to be \( p/(1-k^{-1}) \) (with \( k=2 \) in dendritic trees).](image)

Typically, the density of spines (i.e., the number of spines per unit length along the dendritic channel) quickly saturates after a distance of about 50–100 \( \mu \)m from soma [32, 35, 36]. Therefore, we suppose that the residence probability in cages is simply depth-independent. The waiting probability at each node is an effective measure for the signal input (see the inset of Fig. 2). The analytical procedure is however similar for other initial conditions. We estimate the mean time required for a particle to escape the dendrite structure characterized by the set of parameters \( \{q, p, r, δ\} \) and reach the soma, by treating the soma as an absorbing boundary. However, one can follow the proposed approach to investigate the first-passage time for the inverse direction (i.e., soma-to-spine signaling) as well, by distributing the absorbing boundaries along the tree.

Let us introduce the probability distribution \( P_n(t) \) of being at depth level \( n \) at time step \( t \) (In an irregular structure, the probability of being at each node can be considered instead). The signals initially enter the system via spines, which are almost uniformly distributed along dendritic trees. As a result, the input rate may even exponentially grow with depth, corresponding to the initial condition \( P_0(t) = δ_{n=1} \) (\( n \geq 1 \)). Here for simplicity we consider entering from the dead ends \( P_{n=0} = δ_{n,d} \), which gives the major contribution to the signal input (see the inset of Fig. 2).

The detailed calculations to obtain an expression for the escape-time distribution \( F(t) \) by solving the above set of equations are presented in the *Appendix.*
is a polynomial of maximum degree and the dashed line represents the leading exponential term of Eq. \ref{eq:8} for $t \gg 1$. Inset: $F(t)$ for the same set of parameter values as in the main panel, but for different initial conditions of entering the tree. The solid, dashed, and dotted lines correspond to the initial conditions $P_1(0) = \delta_{q<d}$ (i.e. entering from the dead ends), $P_2(0) = \delta_{r=1}$ (entering from the soma), and $P_3(0) = (2^n - 1)/(2^{d-1})$ (entering uniformly along the tree), respectively.

**FIRST-PASSAGE PROPERTIES**

The overall shape of the escape-time distribution is shown in Fig. 2. Notably, $F(t)$ exhibits an exponential tail. We checked that the exponential decay holds independently of the choice of the trapping factor $q$, the boundary condition $r$ at the deepest branch level, or the chance $p$ of hopping to shallower layers. The slope however varies with $q$, $p$, $r$, and $d$. Importantly, the inset of Fig. 2 shows that while the initial conditions of entering the tree may considerably influence the overall shape of $F(t)$, the slope of the exponential tail remains independent of the way the signals enter the system. It is technically difficult to extract the tail behavior of $F(t)$ from Eq. \ref{eq:8} (see Appendix) in general, however, for a given set of parameter values one can deduce the exponential asymptotic scaling. The resulting dashed line in Fig. 2 fully captures the asymptotic slope. As a proof of the existence of exponential tail, one can show from Eq. \ref{eq:8} that the $z$ transform of the first-passage time distribution can be written as $F(z) = \sum_{k=1}^d (q r)^k$, where $\Phi_k(z)$ is a polynomial of maximum degree $d$. By evaluating the roots $k$ of the polynomial, it can be verified that $F(z) \sim k(1 - \alpha_k z)^{\delta_k}$, where $\alpha_k$ is a function of the structural parameters $d^*, \beta_\leq d$. Then, after partial fraction decomposition of $F(z)$ and inverse transform, $F(t)$ can be represented as a sum of $\alpha_k^t$ terms, thus, can be approximated by the leading exponential term $\alpha_k^t$ in the limit $t \to \infty$.

The mean-first-passage time $\langle t \rangle$ of chemical signals to reach the soma, which is our main quantity of interest, can be evaluated from $F(t)$ as explained in details in the Appendix. The analytical Eq. \ref{eq:9} in the Appendix represents the mean-first-passage time in terms of the coarse-grained model parameters. Although the expression is continuous, it is indeterminate at $p = 1/2$. By taking the limit we get $\langle t \rangle = \sqrt{d - rd + rd^2}$ for the specific choice $p = 1/2$. Crossover in asymptotic scaling behavior—To clarify how $\langle t \rangle$ varies with the model parameters, we exclude the indeterminate point $p = 1/2$ to simplify the MFPT expression. For $p \neq 1/2$, Eq. \ref{eq:10} of the Appendix reduces to the sum of a linear and an exponential function of $d$,

$$\langle t \rangle = \frac{d}{q(2p - 1)} + \frac{p r - pq(2p - 1)}{q r(2p - 1)^2} \left(\frac{1}{p - 1}d - 1\right).$$

Hence, $\langle t \rangle$ in the limit $d \gg 1$ scales exponentially (linearly) for $0 < p < 1/2$ ($1/2 < p < 1$), as the exponential term on the right-hand side of Eq. \ref{eq:10} dominates (vanishes). It can be also seen that $\langle t \rangle$ for the specific choice $p = 1/2$ scales as a power-law $d^\gamma$ with $\gamma = 2$. Thus, the crossover of the asymptotic mean escape time from a power-law to an exponential scaling can be summarized as

$$\langle t \rangle \sim \begin{cases} \frac{1}{q(2p - 1)} d, & 1/2 < p < 1, \\ \frac{1}{q r(2p - 1)^2} e^{d \ln (\frac{1}{p} - 1)}, & 0 < p < 1/2. \end{cases}$$

FIG. 3. Mean escape time vs the depth of the tree for (a) $p < 1/2$ (log-log scales) and (b) $p \geq 1/2$ (log-log scales) at $q = r = 1$. The analytical results of Eq. \ref{eq:9} are shown with solid lines, and the dashed lines represent the asymptotic exponential or power-law scaling of $\langle t \rangle$ via Eq. \ref{eq:10}. The change in the scaling behavior of $\langle t \rangle$ from linear to exponential at the threshold value $p_c = 1/2$ in a 1D random walk can be understood because the effective direction of flow (with respect to the target) is inverted. This also induces a transition from recurrent to transient
random walks in infinite trees \[41\]. At \(p=\frac{1}{2}\), the balance between the two directions of diffusive transport holds and it is expected that the bias parameter \(p\) in a healthy neuron is around this threshold value.

RESULTS AND DISCUSSION

**Coarse-grained model calibration**

In the following, we compare our analytical results to those obtained from ordinary diffusion at microscopic scales in dendritic spines and other relevant geometries such as thickening tubes, to verify the applicability of our coarse-grained approach and to calibrate the model parameters. Note that the diffusion problem with a constant diffusion coefficient across the structure is basically a linear differential equation. If the trend of the first-passage time versus one of the model parameters or as a function of a related geometrical characteristic of actual dendrite structures match, then our model parameter can be calibrated into the dendritic structure through a fit to micro-scale computations for pure diffusion.

The structure of neuronal dendrites primarily depends on the nervous system and varies in different neuronal regions and cell types. However, as a reference for comparison, here we have chosen typical cerebellar Purkinje cells of guinea pigs which extend nearly 200 \(\mu\)m from the soma and have \(\sim 450\) dendritic terminals \[12\]. Thus, there are nearly 10 generations of junctions in such a structure (corresponding to \(d=10\) in our coarse-grained view) and they branch out every 20 \(\mu\)m on average.

**The bias parameter \(p\):** The problem of diffusion in a tube of varying cross section has been thoroughly studied both theoretically and numerically in the literature \[43\]. Particularly, Brownian dynamics simulations at microscopic scales were employed in \[44\] to explore the range of validity of an effective one-dimensional description of diffusion in uniformly thickening or thinning tubes. Denoting the opening angle of the tube with \(\theta\) [see the inset of Fig.\[4\]a)], they approximated the mean-first-passage time \((t)\) between the two ends of a tube of length \(L_{\text{tube}}\) and initial radius \(R_{\text{tube}}\), scaled by \((t)\) of a tube of uniform cross section, as

\[
\frac{(t)}{(t)_{\text{uniform}}} \simeq \begin{cases} \frac{1+\lambda^2}{3} (3+2\lambda \bar{L}), & \lambda<0, \\ \frac{1+\lambda^2}{3} \frac{3}{1+\lambda \bar{L}}, & 0<\lambda, \end{cases}
\]

where \(\lambda = \tan \theta\) and \(\bar{L}=L_{\text{tube}}/R_{\text{tube}}\). Their analytical and simulation results match for opening angles \(\theta<10^\circ\). Even such small thickening rates are still larger than what is typically observed in neuronal dendrites. For example, the thickness of the dendritic channel varies from nearly 0.5 around the dead ends to less than 8 \(\mu\)m close to soma in cerebellar Purkinje cells of guinea pigs which has a typical extent of 200 \(\mu\)m, i.e. an opening angle of less than \(2^\circ\) \[42\]. Therefore, within the validity range of their analytical expressions, we compare \((t)\) obtained from our coarse-grained approach Eq.\[9\] to their results in Fig.\[1\]a).

We set \(q=r=1\) to avoid trapping since Eq.\[4\] is valid for smooth tubes with reflecting walls. We also consider our reference dendritic structure [see Figs.\[4\](b),(e)] for ease of comparison. The scaled MFPTs obtained via Eqs.\[9\] and \[1\] fit very well using a simple linear map between \(\lambda\) and \(p\) as \(\lambda \sim 0.5p-0.25\). We checked that, within biologically relevant parameter ranges and weakly thickening regime \(\theta<5^\circ\), one can obtain similar satisfactory agreement between the mean first-passage times by treating the coefficients of the linear transformation as fit parameters. In the following, we choose \(p=0.55\) as the reference value for our coarse-grained bias parameter in a typical healthy dendrite (corresponding to \(\theta\approx1.4^\circ\)). Note that the geometry of the junctions may affect the first passage results in general, however, we expect that it causes minor variations since the cross-section area at the branch point is conserved.

**The trapping parameter \(q\):** The coarse-grained parameter \(q\) in our model indeed represents the fraction of time spent in the dendritic channel in the steady state, which is set by the probabilities \(\kappa_w\) and \(\kappa_m\) of switching from motion in the channel to waiting in the spines and vice versa. \(\kappa_w\) is proportional to the density of spines and the mean entrance area of the spine neck and inversely proportional to the cross-section area of the dendritic channel. Thus, one obtains \(\kappa_w \propto \rho R_{\text{neck}}^2 / V_{\text{neck}}^2\), where \(R_{\text{neck}}\) and \(V_{\text{neck}}\) denote the neck radius, spine density and radius of the dendritic channel, respectively. \(\kappa_m\) is inversely proportional to the mean escape time from spines \((t)_{\text{spine}}\), which obeys \[21\]

\[
(t)_{\text{spine}} = \frac{L_{\text{neck}}^2}{2D} + \frac{L_{\text{neck}}^2}{D} \frac{V_{\text{head}}}{V_{\text{neck}}} + \frac{V_{\text{head}}}{4DR_{\text{neck}}}, \tag{5}
\]

with \(D\) being the diffusion coefficient and \(L_{\text{neck}}, V_{\text{neck}}\) and \(V_{\text{head}}\) denoting, respectively, the neck length and volume and the head volume of the spines. The diffusion coefficient depends on the size of the diffusing object. For example, the typical value of \(D\) in dendritic spines for Ca\(^{2+}\) ions and green fluorescent protein (GFP) variants (that are much smaller in size) were reported to be \(\sim 100\) and 20 \(\mu\)m\(^2\)/s, respectively \[45\]. Inside the dendritic channel, \(D \sim 37\mu m^2/s\) was obtained for a specific photoactivatable GFP (paGFP) \[14\]. Similar results were reported for diffusion in other cell types. For comparison, \(D\) was found to be \(\sim 23.5\) and 25.2 \(\mu m^2/s\) for the motion of enhanced GFP (eGFP) inside the nucleus and in the cytoplasm of HeLa cells, respectively \[40\]. For a typical thin spine \[17\] with \(R_{\text{neck}}=100\, \text{nm}, L_{\text{neck}}=1\, \text{mm},\) and a head diameter of 1 \(\mu\)m (thus with \(V_{\text{neck}}\approx 0.03 \mu m^3\) and \(V_{\text{head}}\approx 0.52 \mu m^3\)) as shown in Fig.\[1\]b), one gets \((t)_{\text{spine}}\approx 0.19, 0.48,\) and 0.77 sec for the escape time of Ca\(^{2+}\), paGFP, and eGFP from spines (using \(D_{\text{Ca}}=100, D_{\text{paGFP}}=40,\) and \(D_{\text{eGFP}}=25 \mu m^2/s\)). Moreover, the mean travel times of signals from synapses to soma in smooth dendritic channels of length \(x\) can be estimated from Eq.\[4\] as \(t \approx \sqrt{x}\). By choosing \(x=20 \mu m\) as an example, one obtains 2.0, 5.0, and 8.0 sec for the travel time of Ca\(^{2+}\), paGFP, and eGFP, respectively.
The transitions between the two states of motility are non-Markovian in general, however, one can estimate the asymptotic value of $q$ in the limit $t \to \infty$ as a function of the volumes of the dendritic tube and spines as

$$q = \frac{\kappa_m}{\kappa_m + \kappa_w} \approx \frac{V_{\text{tube}}}{V_{\text{tube}} + V_{\text{spines}}} = \frac{1}{1 + \frac{\rho}{\pi R_{\text{tube}}^2} (V_{\text{head}} + V_{\text{neck}})}.$$  

Figure 4(c) shows how the parameter $q$ varies with the spine density and volume. While increasing $\rho$ or $V_{\text{spine}}$ enhances the trapping probability and thus reduces $q$, increasing the volume of the dendritic tube leads to longer excursion times in the tube and increases $q$, as shown in Fig. 4(d). By choosing $\rho = 2 \frac{\mu m}{\mu m}$, $R_{\text{tube}} = 1 \mu m$, and $V_{\text{head}} + V_{\text{neck}} \approx 0.55 \mu m^3$, we obtain the healthy reference value $q \approx 0.74$ for further comparisons.

The boundary-condition parameter $r$: Finally, we calibrate the parameter $r$ via a similar procedure as explained for $q$. The coarse-grained parameter $r$ effectively represents the probability of motion inside the segment of the dendritic tube which connects the last branch point to the dead end [see the schematic Fig. 4(e)]. By ignoring the minor corrections due to the negligible thickening along such a short tube segment, the asymptotic value of $r$ can be approximated as

$$r \approx \frac{V_{\text{tube}}}{V_{\text{tube}} + V_{\text{spines}} + V_{\text{dead-end}}} \approx \frac{1}{1 + \frac{\rho}{\pi R_{\text{tube}}^2} (V_{\text{head}} + V_{\text{neck}}) + \frac{V_{\text{dead-end}}}{\pi R_{\text{tube}}^2 L_{\text{tube}}}}.$$  

Let us consider a spherical dead end with a typical diameter of 3 $\mu m$ and assume that the tree branches out every 20 $\mu m$ on average. Then, using the rest of the reference parameter values used for the determination of the $q$ parameter, we get $r \approx 0.63$. The variation of $r$ as a function of the volume of the dead end is shown in Fig. 4(f). Even in the absence of the dead end (i.e. $V_{\text{dead-end}} = 0$), the signals may be still trapped in the spines distributed between the dead end and the last junction, leading to $r \neq 1$.

**Influence of pathological changes on transmission of chemical signals**

After adopting the set of model parameter values $p = 0.55$, $q = 0.7$, $r = 0.6$ and $d = 10$ as the reference for healthy structures of dendrites, next we investigate how far the mean-
first-passage time varies when the geometrical characteristics of the dendritic structure evolve during the course of aging or neurodegenerative disease progression. Here we choose aging and a few examples of neurodegenerative disorders (such as Alzheimer’s disease, schizophrenia, and fragile X and Down’s syndromes), for which, clear trends for the pathological changes of dendritic structure have been reported in the literature [48]. In the course of aging or Alzheimer’s progression, both the density of spines and the extent of the dendritic tree reduce [6, 12, 49] (The spine density of the apical dendrites of pyramidal neurons in the cingulate cortex of humans may decrease to less than 60% with aging [6]). These changes are equivalent to the increase of $q$ and reduction of $d$ in our coarse-grained perspective. It is also known that the schizophrenia and Down’s syndrome progression leads to the reduction of the spine size [50, 51], corresponding to the enhancement of our $q$ parameter. The pathology of fragile X makes the prediction of MFPT variations complicated. In the course of fragile X progression, while the spine density increases (enhancement of $q$), their shapes become more elongated and the spine head volume reduces (reduction of $q$) [52–54]. Therefore, we expect that the variation of $q$ (and thus of the MFPT) is less pronounced in fragile X compared to the other examples. The competition between the variations of spine density and shape determines whether $q$ effectivity decreases or increases in the course of fragile X progression.

In Fig. 5 we show the trends of the MFPTs upon changing the dendritic structure due to aging or diseases, as explained above. The combined effects of the reduction of tree extent and spine density due to aging or Alzheimer’s disease can dramatically decrease the MFPT of chemical signals from the synapses to the soma [Fig. (a)]. To calculate the MFPT, we used Eq. (9) with $q$ inserted from Eq. (6) and $d = L (\mu m)/20$. The reduction of both spine density and tree extent to half of their healthy reference values decreases the relative MFPT to $(t)/(t)_{\text{healthy}} \approx 0.3$. Thus, the system gradually loses the abil-
ity to compartmentalize ions and molecules and maintain chemical concentrations to a wide extent. The shrinkage of the spine size in schizophrenia and Down’s syndrome leads to a similar trend for the variation of MFPT, however, the effect is less pronounced. In the extreme case of zero head volume, the MFPT reduces to nearly 80% of its reference value (see panel (b) of Fig. 5). As a result of the competition between the increase of spine density (up to \( \rho = 10 \) spines/\( \mu m \)) and reduction of spine head volume (down to \( R_{\text{head}} = 0 \)) in fragile X syndrome, the relative MFPT, \( \langle t \rangle /\langle t \rangle_{\text{healthy}} \), may vary within the range of \([0.6, 1.9]\). If the reduction rate of spine head volume equals the growth rate of spine density, the two effects compensate each other and the MFPT remains unchanged, as shown by the contour line in Fig. 5(c). In other neurodegenerative disorders, the pathology of spine and dendrite structure is more complicated. For example, distortion of spine shape in most mental retardations [10] makes the prediction of the MFPT trend difficult. Another point is that there is currently a lack of quantitative studies to clarify the impact of diseases or aging on the thickening of dendritic tubes (corresponding to the variation of our \( p \) parameter) or on the morphological changes of growth cones (variation of \( r \)). In Fig. 4(d), we calculate the MFPTs within reasonable variation ranges of the opening angle of the dendritic tube or the radius of spherical growth cones. Here we use Eq. 9 with \( q \) inserted from Eq. 9 and \( p \) from the linear relation \( \tan(\theta) \approx 0.5p - 0.25 \). One obtains up to 3-fold increase or reduction in \( \langle t \rangle \) compared to the healthy reference \( \langle t \rangle_{\text{healthy}} \).

The mean travel time of chemical signals in dendrites reflects the ability to preserve local concentrations or induce concentration gradients of ions and molecules, thus, it is tightly connected to neural functions. Therefore, the quantitative evaluation of the first-passage times in different diseases is a step forward towards linking the disease progression to neural functions and draw physiological conclusions.

Structural irregularities

In our analytical formalism, we consider constant coarse-grained parameters along the entire tree. This corresponds to the assumption of a spatially homogeneous structure, i.e. if the dendritic tree is regularly branched, the channels thicken with the same rate throughout the tree, the spine density and size are spatially uniform, and all the growth cones are of the same size. From a coarse-grained perspective, such a regular structure can be described by a few major parameters, which allows for the calculation of the MFPTs. Taking into account that our coarse-grained parameters indeed represent the key structural features which undergo pathological changes in the course of neurodegenerative disease progression, the model enables us to connect the disease progression to signal transmission, as discussed in the previous section. However, realistic dendritic structures are spatially heterogeneous. For example, the density of spines may vary even up to 40% around the global mean value in dendritic trees [6, 33]. The spines also undergo dynamic structural changes regulated by neuronal activity [3].

In view of the realistic structural fluctuations, the basic question is whether the analytical predictions via our coarse-grained approach remain valid when the structural parameters of a given dendritic tree are allowed to spatially vary around their global mean values. In the following, we compare the analytical result for the reference set of parameter values with the simulation results where the structural parameters spatially fluctuate around the reference values. For comparison, the fluctuation range \( \Delta q/\langle q \rangle \approx 0.2 \) is comparable to the realistic variations in spine head size and density in pyramidal neurons in the sinate cortex of humans [3]. Similar fluctuation ranges are considered for \( d \), \( r \) and \( p \) parameters, in the absence of quantitative studies to explore the variation ranges of the extent of dendritic trees, the size of growth cones, and the thickening rate of dendritic channels.

In each of the Monte Carlo simulations, we vary only one of the coarse-grained parameters while the rest of them are fixed at their mean values \((d) = 10 \), \((q) = 0.55 \), \((r) = 0.6 \). Let us first consider the parameters \( p \), \( q \), and \( r \). A new value is assigned to the variable parameter at each random walk step, which is randomly taken from a uniform distribution in the interval \([p - \Delta p, p + \Delta p] \), \([q - \Delta q, q + \Delta q] \), or \([r - \Delta r, r + \Delta r] \) for parameter \( p \), \( q \), or \( r \), respectively. The upper panels of Fig. 6 represent the variation ranges of the geometrical characteristics of dendritic structures as the width of the uniform distributions for coarse-grained parameters vary from 0 up to 20% around the reference (healthy) values. In the upper panel of Fig. 6(b) we present the extreme values of the spine head volume as a function of \( \Delta q/\langle q \rangle \). However, one can alternatively fix the head volume \((e.g., V_{\text{head}} = 1 \mu m^3) \) and consider the changes in the spine density and get \([1.3, 1.3] \), \([1.1, 1.6] \), \([0.9, 1.8] \), and \([0.6, 2.5] \) intervals for the number of spines per micron at \( \Delta q/\langle q \rangle = 0 \), 0.05, 0.1, and 0.2, respectively. The middle panels show that the resulting escape-time distributions \( F(t) \) invisibly deviate from the analytical prediction (solid line) for \( q \) and \( r \) parameters, while the tail of \( F(t) \) starts deviating from the theory line when \( p \) varies up to 10% around \( \langle p \rangle = 0.55 \). However, such tail deviations have no significant impact on the mean-first-passage time \( \langle t \rangle \), as shown in the lower panel of Fig. 6(a) at \( p = 0.55 \). We also repeated the simulations for other sets of reference parameters to check whether \( \langle t \rangle \) deviates from the analytical prediction. According to the results shown in the lower panels of Fig. 6 we conclude that our analytical results are robust against realistic fluctuations of the structural characteristics across the dendritic trees (even up to 20% around the mean), over a wide range around the reference set of coarse-grained parameter values.

Next, we investigate the variations in the extent of the tree around the mean value \( \langle d \rangle \). To this aim, in Monte Carlo simulations we construct stochastic tree structures.
by randomly allowing the nodes to have their child nodes in a hierarchical manner starting from the root node. The procedure continues until the tree consists of a given number of dead ends. A few examples of the resulting structures with 32 dead ends are shown in Fig. 7(a). We characterize the depth of the irregular tree by the average of its dead-ends depths \( \langle d \rangle \), and its variation by \( \sigma(d) \), with \( \sigma(d) \) being the standard deviation. As shown in Fig. 7(a), the ensemble of structures corresponding to a given \( \sigma(d) \) contains globally heterogeneous configurations as well as highly asymmetric ones. In Fig. 7(b), we show how the deviation from our analytical prediction grows with increasing the fluctuation range of the dead-end depths. It can be seen that the error of the analytical expression remains below 10% even in considerably heterogeneous structures with \( \frac{\sigma(d)}{\langle d \rangle} \approx 20\% \). For lower variations in the extent of the tree \( \langle d \rangle \), the error is less than 5%. Thus, our analytical approach is applicable to dendritic structures with moderate heterogeneity in their branching pattern.

So far, we have investigated the influence of global dynamic irregularities of structure on the first-passage times. However, static local irregularities may also exist in real dendrites, induced by pathological changes. For

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FIG. 6. Comparison between the analytical predictions for constant parameter values and simulation results for dynamically varying (a) \( p \), (b) \( q \), or (c) \( r \) parameter across the dendritic structure. The reference parameter values are taken to be \( p=0.55 \), \( q=0.7 \), \( r=0.6 \) and \( d=10 \). Upper panels: Schematic representation of the variations in the realistic dendritic geometry when the coarse-grained model parameters vary 5, 10 or 20% around their mean reference values. Middle panels: Log-lin plots of the escape-time distribution. The analytical curve via Eq. 8 (solid line) is compared to the simulation results (symbols). The insets are schematic diagrams of typical trees with \( d=5 \) and 10% fluctuations in the corresponding model parameter. The radii of the circles are proportional to the relative deviations from the minimum values. Lower panels: Mean escape time versus the model parameters. The solid line represents the analytical prediction of Eq. 9 and the symbols correspond to the simulation results. \( \langle \ldots \rangle \) denotes averaging over both the ensemble of realizations for a given disorder and the ensemble of possibilities for the stochastic particle dynamics.
example, various dendritic abnormalities associated with fibrillar amyloid deposits in transgenic mouse model of Alzheimer’s disease and in human brain were reported in [57]. Extensive spine density loss, shaft atrophy (i.e. decline in the radius of the dendritic tube), and formation of varicosity (which consists of an enlarged tortuous and crumpled part of dendritic channel) were observed in the vicinity of amyloid deposits. From our coarse-grained perspective, the local varicosity formation, shaft atrophy and spine-density reduction correspond, respectively, to the decrease of $q$ and $p$ and increase of $q$ in a specific region of the tree such as a sub-branch. To elucidate the impact of static local irregularities on signal transmission, our effective 1D analytical description based on the depth levels does not help. Therefore, we construct the entire tree structure in Monte Carlo simulations again (similar to the procedure to construct asymmetric configurations in Figure [7] but this time for $q$ or $p$ parameters). Figure 5 shows a few samples of coarse-grained dendritic trees with an affected sub-branch. We change $q$ or $p$ parameter in the affected sub-branch, while keeping the rest of parameters the same as the entire tree. By imposing a constant entrance rate (one particle from one of the randomly chosen dead ends at each time step), we eventually obtain the spatial distribution of non-interacting particles in the steady state. The results shown in Figure 5 reveal that local structural irregularities influence the transport of particles and lead to the formation of heterogeneous density patterns in the system. Reduction of $q$ or $p$ in the affected sub-branch to $q = 0.1$ or $p = 0.3$ imposes a local trap and leads to a local population which is, respectively, 43% or 28% higher than the homogeneous case. On the other hand, increasing the local $q$ to $q = 1$ reduces the population in the sub-branch to 88% compared to the regular tree. Such uneven distributions of signaling ions and molecules may have dramatic consequences on neural activities such as neuronal firing and the ability to maintain chemical concentrations and gradients.

**CONCLUSION AND OUTLOOK**

In summary, an analytical framework has been developed to obtain first-passage times of chemical signals in neuronal dendrites in terms of the structural factors which undergo pathological changes in the course of neurodegenerative disease progression. By quantitatively connecting the dendritic structure to signal transmission, our results open the possibility to establish a direct link between the disease progression and neural functions, which allows to draw important physiological conclusions.

To consider structural inhomogeneities and dynamical variations of real dendrites, the master equations can be generalized by introducing uncorrelated probability distributions for the key structural parameters $p$, $q$, and $r$ and calculating the first-passage properties in terms of their first two moments. The fluctuation of depth $d$ can be also taken into account by distributing the dead-end conditions among the master equations which belong to a given range of the deepest levels of the tree. Moreover, the MFPT of passive particles in crowded dendritic channels or active ones along microtubules can be taken into account in our master equations by introducing a (anti-)persistent random walker. The interparticle interactions at high density regimes affect the transport through the narrow necks of spines, which influences the waiting time distribution in spines and the first-passage properties. The investigation of these aspects calls for additional research efforts. The proposed approach provides an analytical route into a variety of search and transport phenomena on complex networks (e.g. weighted time-varying trees), branched macromolecules and polymers, various energy landscapes, and more generally biased random walks with absorbing...
FIG. 8. Upper panels: Schematic diagrams of example trees with local structural irregularities in the sub-branch starting from junction \(i\). Common parameters (unless locally varied): \(d=6\), \(p=0.55\), \(q=0.7\), and \(r=0.6\). The modified coarse-grained parameter in the sub-branch is denoted by \(q_i\) or \(p_i\). The radii of the circles are proportional to the local \(q\) (a,b) or \(p\) (c) values.

Lower panels: Heat maps of the stationary density of particles in each branch in simulations performed for the corresponding asymmetric structures.

boundaries \[57\]. Our calculations can be adapted to real labyrinthine environments by introducing node-degree distribution and closed paths.

Appendix: first-passage time calculations
To derive an expression for the first-passage time distribution, we start from the master Eqs.\[1\] and obtain a set of equations for \(P_d(z)\) at different depth levels by defining the \(z\) transform \(\mathcal{P}_n(z) = \sum_{t=0}^{\infty} P_n(t) z^t\) (with \(|z|<1\)). For example, the transformation of the last equation in the set of master Eqs.\[1\] reads \(P_d(z) = q(1-p)zP_{d-1}(z)+(1-r)zP_d(z)+1\), where the constant term results from the \(z\) transform of the delta function. The challenge is that the number of equations \(d+1\) is arbitrary. However, after some algebra, we solve this set of equations to obtain \(P_d(z)\), from which the \(z\) transform of the first-passage time distribution to reach the soma can be evaluated as \(F(z) = \sum_{t=0}^{\infty} F(t) z^t = q p z P(z)\) \[58\]. Let us define \(\lambda_\pm = \frac{1}{q p} [1+(q-1)zA(z,q,p)]\), where \(A(z,q,p) = [1+2(q-1)z+[1-2q+(1-2p)^2q^2]z^2]^{1/2}\). We derive the following exact expression for the \(z\) transform of the escape-time distribution,

\[
F(z) = \frac{2^{d+1} r A(z,q,p)}{\left(\lambda_+^d - \lambda_-^d\right) \left[r \left(1-(q-1)z\right) + p q \left(-2+2 z - r z\right)\right] + \left(\lambda_+^d + \lambda_-^d\right) r A(z,q,p)}.
\] \[8\]

Next, by inverse \(z\) transforming of \(F(z)\), one gets an explicit lengthy expression for \(F(t)\) in terms of the number of time steps \(t\). We confirmed the correctness of our calculations by comparing the analytical predictions via Eq.\[8\] to the results of extensive Monte Carlo simulations obtained from \(10^6\) realizations of the same stochastic process. The mean-first-passage time \(\langle t\rangle\) can be evaluated as \(\langle t\rangle = \sum_{t=0}^{\infty} t F(t) = \frac{d}{dz} F(z)\bigg|_{z \to 1}\).
By expanding Eq. 8 around $z=1$ up to first order terms, $F(z) \sim F(z)\left|_{z=1}^{z=1} \right. + (z-1)\frac{d}{dz}F(z)\left|_{z=1}^{z=1} \right. + O((z-1)^2)$, and defining $\gamma_\pm = \frac{1}{p}(1\pm|2p-1|)$ we arrive at the following expression for the mean escape time,

$$\langle t \rangle = 2^{d+1} \left[ \frac{(\gamma_-^d - \gamma_+^d)}{q r} \left[ 2p q + dr (1 - 2p) + 2 pr \right] + (\gamma_-^d + \gamma_+^d) dr |2p-1|^2 \right]$$

where $\Theta(x) = \{ +1 \, \text{if} \, x \geq 0 \, \text{and} \, 0 \, \text{if} \, x < 0 \}$. In the limit $d \to \infty$, $\langle t \rangle$ diverges as expected for infinite Cayley trees \cite{59} and Bethe lattices \cite{41, 50}.

**AUTHOR CONTRIBUTIONS**

Correspondence and request for materials should be addressed to M.R.S. (email: shaebani@usi.uni-sb.de). L.S. and M.R.S. designed the research. R.J. and M.R.S. performed the research. All authors contributed to the analysis and interpretation of the results. M.R.S. wrote the manuscript.

**ACKNOWLEDGEMENTS**

This work was funded by the Deutsche Forschungsgemeinschaft (DFG) through Collaborative Research Center SFB 1027 (Projects A7 and A8).

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