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Stochastic model of protein receptor trafficking prior to synaptogenesis

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We present a stochastic model of NMDA (*N*-methyl *d*-aspartate) receptor transport along a dendrite prior to synapse formation. Receptors undergo periods of intracellular kinesin motor-driven transport along microtubules interspersed with periods of cycling to the cell surface through exocytosis or endocytsosis. The stochastic dynamics is reduced to a spatially discrete hopping model that determines the time-dependent distribution of receptors along the dendrite. We also investigate how possible defects in motor-assisted transport can affect this distribution.

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I. INTRODUCTION

Identifying the mechanisms that govern chemical synapse formation (synaptogenesis) is of fundamental importance to our understanding of neural development, plasticity, and learning [1,2]. Synapses are sites of cell-to-cell contact that are specialized for the transmission of electrochemical signals between neurons. Synaptic transmission is directional in nature, involving the secretion of neurotransmitter molecules from the presynaptic cell and the subsequent binding to receptors on the postsynaptic membrane. The presynaptic component of a synapse contains hundreds or thousands of neurotransmitter-filled synaptic vesicles together with a so-called active zone. The latter is a protein-rich region of the presynaptic membrane where synaptic vesicles dock, fuse, and release neurotransmitters into the synaptic cleft, the small region between the presynaptic and postsynaptic cells. Directly apposed to the active zone on the postsynaptic side is another protein-dense region known as the postsynaptic density. This structure serves to cluster neurotransmitter receptors beneath the active zone. One of the major issues regarding synaptogenesis is how the various presynaptic and postsynaptic proteins are delivered to a nascent synapse, following the guidance of an axon to a specific dendritic target and the creation of an initial axodendritic contact. This, in turn, requires an understanding of how newly synthesized proteins in the cell body are transported the long distances along axons and dendrites prior to synapse formation. The most common model is that proteins undergo intracellular vesicular transport and are inserted directly into a synapse after a cue initiated by contact between an axon and dendrite. An alternative model is that newly synthesized proteins are inserted into the plasma membrane of an axon or dendrite soon after leaving the cell body and reach a new synaptic site through lateral membrane diffusion.

There is growing experimental evidence to suggest that the assembly of the postsynaptic density differs from that of the presynaptic active zone [3,4], at least in the case of glutamatergic synapses, which are the predominant form of excitatory synapse in the central nervous system. The formation of the active zone is driven by the surface delivery of vesicles containing preassembled presynaptic protein complexes, whereas the construction of the postsynaptic density seems to occur through the sequential recruitment of individual classes of protein. One of the first proteins to appear is NMDA (*N*-methyl *d*-aspartate), which constitutes one of the main types of glutamate receptor. Electron microscopy has established that vesicles containing NMDA clusters are often associated with microtubules, which serve as the substrate for the kinesin family of motor proteins [5–7]. This experimental data is consistent with the intracellular, kinesin-driven transport of NMDA vesicles along microtubules. On the other hand, live cell-imaging data has shown that synapses gradually recruit NMDA receptors, suggesting that there is a diffusional accumulation of NMDA receptors, rather than delivery in discrete vesicular packets [3]. One possible reconciliation of these results is that intracellular vesicles deliver NMDA receptors to the dendritic surface in the vicinity of a synapse, and diffusion then mediates the clustering of synaptic receptors [8]. Interestingly, it has been shown that the transport of NMDA receptors along dendrites is interspersed with periods of immobility during which there is cycling of receptors between the plasma membrane and the cytoplasm via exocytosis (endocytosis) [7] (see Fig. 1). Such cycling would provide a mechanism for delivering the receptors to the dendritic surface, thus making them available for recruitment to synapses.

In this paper, we construct a stochastic model of NMDA receptor trafficking prior to synapse formation, under the as-

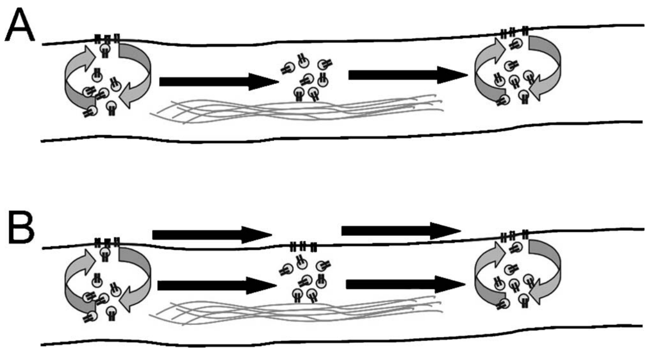

FIG. 1. Two possible scenarios for exocytic (endocytic) cycling and microtubule transport of vesicles containing NMDA receptors prior to synaptogenesis. (A) Intracellular transport interspersed with periods of exocytosis (endocytosis). (B) Simultaneous intracellular and surface transport of NMDA receptors interspersed with periods of exocytosis (endocytosis). (Adapted from Ref. [7]).

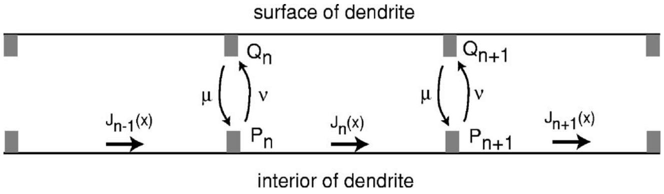

FIG. 2. Compartmental model of NMDA receptor trafficking. Sites of exocytosis (endocytosis) are assumed to be regularly spaced at intervals of length L along a one-dimensional dendritic cable. The spatial extent of each site is assumed to be negligible compared to the interstitial spacing L. Within each site a receptor undergoes transitions between two states, one located in the interior of the dendrite and the other located on the membrane surface. The probability that a receptor at the nth site has been endocytosed (exocytosed) is denoted by P_n (Q_n). In the compartmental regions separating neighboring sites, internalized receptors undergo motor-assisted transport along microtubules with a probability flux $J_n(x)$ at location x, $0<x<L$, within the nth compartment. An internalized receptor can exit a site at a rate K leading to the boundary conditions $J_n(0)=KP_n$.

sumption that the transport process is dominated by intracellular vesicular transport as shown in Fig. 1(a). For simplicity, we take the sites of exocytosis (endocytosis) to be regularly spaced along a one-dimensional dendritic cable. Within each site receptors undergo transitions between two states, one located in the interior of the dendrite and the other located on the membrane surface. Whenever an intracellular receptor (or cluster of receptors) within a vescicle exits a site, it undergoes motor-assisted transport to the next site of exocytosis (endocytosis) along the cable. We show how the stochastic dynamics can be reduced to a system of ordinary differential equations describing the hopping of receptors between neighboring sites of exocytosis (endocytosis), with the net flux into a site determined by the associated Green's function for motor-assisted transport along a microtubule. We solve the resulting equations using Laplace transforms, and determine the time-dependent probability distribution of receptors along the cable.

II. MODEL OF RECEPTOR TRAFFICKING

Consider an infinite one-dimensional dendritic cable that is partitioned into compartments separated by exocytic (endocytic) domains (see Fig. 2). For simplicity, we take each compartment to have the same length L and neglect the spatial extent of each exocytic (endocytic) domain. However, it is straightforward to extend the model to incorporate variations in compartment length. Since we are ignoring surface diffusion of individual receptors, our analysis applies equally well to a vesicle containing a single receptor or a cluster of receptors. A receptor (or receptor cluster) undergoes motor-assisted transport along a microtubule in the interior of each dendritic compartment until it reaches the exocytic (endocytic) domain on the compartment boundary, where it temporarily pauses. Within each exocytic (endocytic) domain, a receptor is in one of two states labeled by $a=1,0$. If $a=1$ then the receptor is located in the interior of the dendrite, whereas if $a=0$ then the receptor is located on the membrane surface. Transitions between the two states are governed by the discrete Markov process $0 \underset{\nu}{\overset{\mu}{\rightleftharpoons}} 1$, where μ is the rate of endocytosis and ν is the rate of exocytosis. If a receptor is in state $a=1$, then it can escape an exocytic (endocytic) zone to the next compartment at some hopping rate K. Let $P_n(t)$, $Q_n(t)$ denote the probability that a receptor is located in the nth exocytic (endocytic) site at time t and is in state $a(t)=1,0$, respectively. Similarly, let $J_n(x,t)$ denote the flux of receptors at location x in the nth compartment at time t with $0\leq x\leq L$. We then have the following system of equations:

$$\frac{dP_n}{dt} = -\nu P_n + \mu Q_n - J_n(0,t) + J_{n-1}(L,t), \tag{2.1}$$

$$\frac{dQ_n}{dt} = \nu P_n - \mu Q_n, \tag{2.2}$$

with $J_n(0,t)=KP_n(t)$.

The flux $J_n(x)$, $0<x\leq L$ is obtained by solving the associated equations for motor-assisted receptor transport within the nth compartment. We will model the latter according to the master equation [9]

$$\frac{\partial p_n}{\partial t} = -\beta p_n + \alpha q_n - v\frac{\partial p_n}{\partial x}, \tag{2.3}$$

$$\frac{\partial q_n}{\partial t} = \beta p_n - \alpha q_n, \tag{2.4}$$

for $0<x\leq L$. Here $p_n(x,t)$ is the probability density that a receptor's vesicle is bound to a microtubule via the associated molecular motor, and is moving with speed v along the filament, whereas $q_n(x,t)$ is the corresponding probability density that the vesicle is unbound and immobile. (We neglect intracellular diffusion of the vesicle in the unbound state.) Transitions between the two states is also governed by a discrete Markov process with α the rate of binding to a microtubule and β the rate of unbinding. The transition rates are assumed to be uniform throughout a compartment. Equations (2.3) and (2.4) are supplemented by the boundary condition

$$J_n(0,t) \equiv KP_n(t) = vp_n(0,t). \tag{2.5}$$

Equations (2.3)–(2.5) can be solved using Laplace transforms (see Appendix and Ref. [10])

$$p_n(x,t) = \frac{K}{v}\int_0^t G(x,t-t'-x/v)P_n(t')dt',$$

where $G(x,t)$ is the Green's function

$$G(x,t) = e^{-\beta x/v}\left[\delta(t) + e^{-t\alpha}\sqrt{\frac{\alpha\beta x}{vt}}I_1(2\sqrt{\alpha\beta xt/v})\Theta(t)\right], \tag{2.6}$$

with Θ a Heaviside function and I_1 a modified Bessel function. Given the solution of $p_n(x,t)$ in terms of $P_n(t)$ for 0

$<x\leqslant L$, we set $J_{n-1}(L,t)=vp_{n-1}(L,t)$ in Eq. (2.1) to obtain the discrete hopping model

$$\frac{dP_n}{dt} = -\nu P_n + \mu Q_n + K[G * P_{n-1} - P_n], \tag{2.7}$$

$$\frac{dQ_n}{dt} = \nu P_n - \mu Q_n, \tag{2.8}$$

with

$$G * P_{n-1}(t) = \int_0^t G(L,t-t'-L/v)P_{n-1}(t')dt'. \tag{2.9}$$

III. ANALYSIS OF MODEL

Equations (2.7) and (2.8) determine the time-dependent distribution of receptors amongst the various discrete sites of exocytosis (endocytosis). Of particular relevance to synaptogenesis is the probability $Q_n(t)$ that a receptor is located in the plasma membrane of the nth exocytic (endocytic) site at time t, since a surface receptor can detect chemicals such as glutamate that may trigger the formation of a synapse [2]. Suppose that a receptor is initially injected into the interior of the dendrite at site $n=0$ so that we have the initial conditions $P_n(0)=\delta_{n,0}$, $Q_n(0)=0$. In order to gain analytical insights into the basic behavior of the system, we will assume for the moment that the rates of exocytosis (endocytosis) are faster than the escape rate from an exocytic (endocytic) domain, that is, $\mu,\nu \gg K$. We can then reduce Eqs. (2.7) and (2.8) to a single scalar equation by carrying out a quasi-steady-state approximation along analogous lines to a recent study of a stochastic gating model [11]. Experimental data suggests that ν,μ are at least comparable to K, since receptors appear to undergo at least one cycle of exocytosis (endocytosis) before being transported to the next site [7]. Having carried out the lowest-order quasi-steady-state approximation, we will then relax our simplifying assumption and analyze the large-t behavior of the receptor distribution.

A. Quasi-steady-state approximation

First, we introduce a dimensionless time by setting $\tau = Kt$ and define the small parameter $\varepsilon = K/(\mu+\nu)$. We also set $a=\mu/(\mu+\nu)$, $b=\nu/(\mu+\nu)$ such that $a+b=1$. Equations (2.7) and (2.8) become

$$\frac{dP_n}{d\tau} = \frac{1}{\varepsilon}\{-aP_n + bQ_n\} + G * P_{n-1} - P_n, \tag{3.1}$$

$$\frac{dQ_n}{d\tau} = -\frac{1}{\varepsilon}\{-aP_n + bQ_n\}. \tag{3.2}$$

We now introduce the change of variables

$$V_n = P_n + Q_n, \quad W_n = aP_n - bQ_n, \tag{3.3}$$

so that

$$P_n = aV_n + W_n, \quad Q_n = bV_n - W_n. \tag{3.4}$$

In terms of the new variables, we have

$$\frac{dV_n}{d\tau} = G * \{aV_{n-1} + W_{n-1}\} - aV_n - W_n, \tag{3.5}$$

$$\frac{dW_n}{d\tau} = -\frac{1}{\varepsilon}W_n - b[G * \{aV_{n-1} + W_{n-1}\} - aV_n - W_n]. \tag{3.6}$$

There is a clear fast-slow separation of variables, and we can take W_n to be in a quasisteady state, that is,

$$W_n = -\varepsilon ab[G * V_{n-1} - V_n] + O(\varepsilon^2). \tag{3.7}$$

Substitution into Eq. (3.5) gives

$$\frac{dV_n}{d\tau} = a[1-\varepsilon b][G * V_{n-1} - V_n] + O(\varepsilon^2). \tag{3.8}$$

In terms of the original temporal units, we have

$$\frac{dV_n}{dt} = \bar{K}\left[1 - \frac{\nu\bar{K}}{\mu(\mu+\nu)}\right][G * V_{n-1} - V_n] + O(\varepsilon^2), \tag{3.9}$$

with

$$\bar{K} = \frac{\mu K}{\mu+\nu}, \tag{3.10}$$

the mean hopping rate from an exocytic (endocytic) site. Given the solution for V_n the corresponding probabilities P_n, Q_n are, to lowest order,

$$P_n = \frac{\mu}{\mu+\nu}V_n, \quad Q_n = \frac{\nu}{\mu+\nu}V_n. \tag{3.11}$$

Under the above quasi-steady-state approximation, the pair of equations (2.7) and (2.8) have been reduced to the single equation (3.9). The latter can be solved straightforwardly using Laplace transforms. Defining $\hat{V}_n(s) = \int_0^\infty e^{-st}V_n(t)dt$ we have

$$\hat{V}_n(s) = \frac{[\Lambda \hat{G}(L,s)e^{-sL/v}]^n}{(s+\Lambda)^{n+1}}, \tag{3.12}$$

with $\hat{G}(x,s)$ the Laplace-transformed Green's function (see Appendix)

$$\hat{G}(x,s) = e^{-s\beta x/[s+\alpha]v}\Theta(x) \tag{3.13}$$

and

$$\Lambda = \bar{K}\left[1 - \frac{\nu\bar{K}}{\mu(\mu+\nu)}\right]. \tag{3.14}$$

Inverting the Laplace transforms in Eq. (3.12) using the convolution theorem, we find that

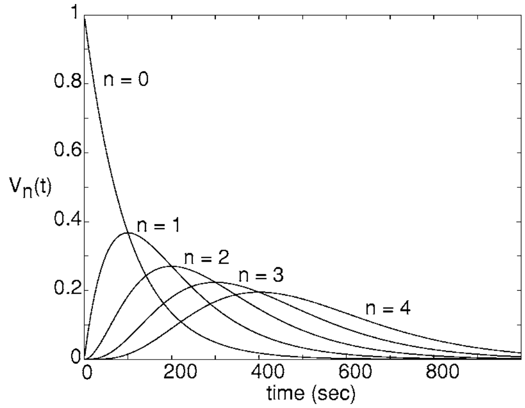

FIG. 3. Plot of $V_n(t)$ as a function of t for $n=0,1,2,3$ in the case of pure ballistic transport ($\beta=0$). Spacing between exocytic (endocytic) sites is $L=5$ μm and the speed of motor-assisted transport is $v=1$ $\mu\text{m s}^{-1}$. The hopping parameter is $\Lambda=0.01$.

$$V_n(t)=\int_0^t G(nL,t-t'-nL/v)\frac{(\Lambda t')^n}{n!}e^{-\Lambda t'}dt'. \quad (3.15)$$

Substituting for G using Eq. (2.6) and setting $\chi=\beta L/v$ finally gives

$$V_n(t+nL/v)=e^{-n\chi}\left[\frac{(\Lambda t)^n}{n!}e^{-\Lambda t}+\int_0^t e^{-\alpha(t-t')}\sqrt{\frac{n\chi}{\alpha(t-t')}}\times I_1[2\sqrt{n\chi\alpha(t-t')}]\frac{(\Lambda t')^n}{n!}e^{-\Lambda t'}\alpha dt'\right], \quad (3.16)$$

for $t>0$ and zero otherwise.

First, consider the case of pure ballistic transport ($\beta=0$), in which the vesicles remain bound to the microtubules during motor-assisted transport. (Under normal operating conditions this will be a good approximation if more than one kinesin motor is involved in the transport of each vesicle, since individual kinesin motors have a high duty ratio [12].) We then have

$$V_n(t+nL/v)=\frac{(\Lambda t)^n}{n!}e^{\Lambda t}, \quad t>0. \quad (3.17)$$

The typical spacing between sites of exocytosis (endocytosis) is $L=5$ μm, and the mean time τ_0 for receptors to travel from one site to the next is approximately 1 min [6,7]. A typical mean speed for the motor-assisted transport of vesicles along microtubules is $v=1$ $\mu\text{m s}^{-1}$ [12]. This implies that $L/v \ll \tau_0$ and hence that $K\approx 1$ min^{-1}. Taking $\Lambda=0.01$, we plot $V_n(t)$ given by Eq. (3.17) as a function of t in Fig. 3. This illustrates how the time-to-peak of the total receptor probability at site n is an increasing function of n, whereas the amplitude of the peak decreases with n. Note for the displayed values of n, $n>0$, the shift nL/v is much smaller than the time-to-peak of the distribution $V_n(t)$.

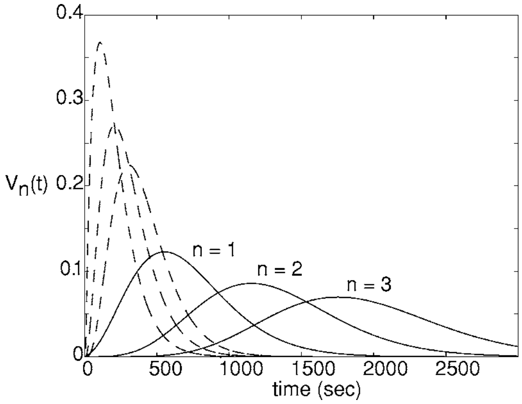

FIG. 4. Plot of $V_n(t)$ as a function of t for $n=0,1,2,3$. Parameter values are $L=5$ μm, $v=1$ $\mu\text{m s}^{-1}$, $\alpha=0.01$, $\chi=5$, and $\Lambda=0.01$. Corresponding results for pure ballistic transport ($\beta=0$) are shown as dashed curves.

Although in a healthy cell the kinesin-based transport of vesicles is processive, there is accumulating evidence that a number of neurodegenerative diseases involve some sort of disruption in the trafficking of organelles along microtubules [13–15]. One possible form of disruption is a slowing down of the transport due to a reduction in the duty ratio of the motors. In our particular model, this would correspond to an increase in the unbinding rate β and/or a decrease in the binding rate α. Suppose that $\beta=1$ s^{-1} and $\alpha=0.01$ s^{-1}. (A typical binding rate under normal conditions is $\alpha=1$ s^{-1} [9].) Now the receptor distribution $V_n(t)$ is determined by numerically evaluating the right-hand side of Eq. (3.16). The results are shown in Fig. 4. It can be seen that the slowing of the motor transport slows down and spreads out the accumulation of receptors at an exocytic (endocytic) region. This differs from what would be observed if the rates of binding (unbinding) were unaltered but the processive speed v of the molecular motors was reduced. In the latter case, the curves in Fig. 3 would undergo an n-dependent shift to the right due to an increase in the delay nL/v. One of the consequences of a reduction in the surface-receptor concentration is that less receptors are available for recruitment to nascent synapses via lateral membrane diffusion, say, and thus there could be a disruption in synaptogenesis.

B. Large-*t* behavior

A useful way to characterize the statistics of the receptor distribution is in terms of the various moments of the site index n. In order to calculate these moments, we introduce the generating function

$$\Gamma(\lambda,t)=\sum_{n=0}^{\infty}e^{\lambda n}[P_n(t)+Q_n(t)]. \quad (3.18)$$

The total probability of being at one of the exocytic (endocytic) zones is then $\Gamma(0,t)$. Since there is a nonzero probability that receptors also undergo ballistic motion between cycles of exocytosis (endocytosis), it follows that $0<\Gamma(0,t)<1$. Hence, defining the normalized kth-order moment according to

$$\langle n^k\rangle(t) = \frac{1}{\Gamma(0,t)}\sum_{n=0}^{\infty} n^k[P_n(t)+Q_n(t)], \tag{3.19}$$

the corresponding cumulants are given by

$$C_k(t) = \left.\left(\frac{d}{d\lambda}\right)^k \ln \Gamma(\lambda,t)\right|_{\lambda=0}, \tag{3.20}$$

with $C_1(t)=\langle n\rangle(t)$ and $C_2(t)=\langle \Delta n^2\rangle(t)$, etc. The large-$t$ behavior of the cumulants can be obtained by considering the small-s behavior of the corresponding Laplace transform $\hat{\Gamma}(\lambda,s)$.

We will calculate $\hat{\Gamma}(\lambda,s)$ using the original pair of equations (2.7) and (2.8), rather than performing a quasi-steady-state approximation. Laplace transforming these equations gives

$$\hat{P}_n(s) = \frac{[K\hat{G}(L,s)e^{-sL/v}]^n}{[\xi(s)+K]^{n+1}},$$

$$\hat{Q}_n(s) = \frac{\nu \hat{P}_n(s)}{s+\mu}, \quad n \geqslant 0, \tag{3.21}$$

with $\xi(s)=s(s+\mu+\nu)/(s+\mu)$ and $\hat{G}(x,s)$ defined by Eq. (3.13). Inverting the Laplace transforms in Eq. (3.21) using the convolution theorem and performing a Bromwich contour integral, we find that

$$Q_n(t) = \int_0^t G(nL,t-t'-nL/v) \times [F_n^{+}(t')e^{\lambda_+ t'} + F_n^{-}(t')e^{\lambda_- t'}]dt', \tag{3.22}$$

with $F_n^{\pm}(t)$ given by nth-order polynomials in t;

$$F_n^{\pm}(t) = \left.\frac{\nu K^n}{n!}\left(\left[\frac{d}{ds}+\lambda_{\pm}t\right]^n \frac{(s+\mu)^n}{(s-\lambda_{\mp})^{n+1}}\right)\right|_{s=\lambda_{\pm}},$$

where

$$\lambda_{\pm} = \frac{1}{2}[-(\mu+\nu+K) \pm \sqrt{(\mu+\nu+K)^2-4\mu K}].$$

Substituting Eq. (3.21) into the Laplace transform of Eq. (3.18) and summing the resulting geometric series leads to the result

$$\hat{\Gamma}(\lambda,s) = \frac{\xi(s)}{s}\frac{1}{\xi(s)+K[1-e^{\lambda}\hat{G}(L,s)e^{-sL/v}]}. \tag{3.23}$$

Keeping only the most singular terms in s and using a Tauberian theorem [16], we find that in the large-t limit

$$L\langle n\rangle \approx \frac{L\bar{K}t}{1+\bar{K}L/\bar{v}}, \tag{3.24}$$

with

$$\bar{v} = \frac{\alpha v}{\alpha+\beta} \tag{3.25}$$

the mean velocity along a microtubule. Similarly,

$$L^2\langle \Delta n^2\rangle \approx Dt, \tag{3.26}$$

with D an effective diffusivity,

$$D = \left\{1 + 2\bar{K}\left[\frac{\mu\nu}{\nu+\mu} + \frac{2\beta\bar{K}L}{\alpha(\alpha+\beta)\bar{v}}\right]\right\}\frac{L^2\bar{K}}{(1+\bar{K}L/\bar{v})^3}. \tag{3.27}$$

Finally, the total fraction of receptors undergoing exocytosis (endocytosis) approaches a constant,

$$\Gamma(0,t) \to \frac{1}{1+\bar{K}L/\bar{v}}, \tag{3.28}$$

as $t\to\infty$.

Under normal trafficking conditions, experimental data suggests that $\bar{K}L/\bar{v} \ll 1$ so that the effective speed of NMDA transport along the dendrite is $Ld\langle n\rangle/dt \approx L\bar{K}$, that is, the transport depends mainly on the mean rate of hopping between exocytic (endocytic) sites. On the other hand, if there were a sufficient reduction in the duty ratio or speed v of the molecular motors such that $\bar{K}L/\bar{v} \gg 1$, then $Ld\langle n\rangle/dt \approx \bar{v}$ and the transport would be determined primarily by the mean speed of the motors. In the case of a low duty ratio there would also be a relatively large diffusivity D.

IV. DISCUSSION

In this paper we have constructed a stochastic model of NMDA receptor trafficking along a dendrite prior to synapse formation. Solutions of the model equations determine the time-dependent distribution of surface and intracellular receptors along the dendrite. We have also examined how defects in motor-assisted transport—a possible contributing factor to various neurodegenerative diseases—can affect this distribution. In particular, the resulting reduction in receptor concentration means that less receptors are available for recruitment at nascent synapses, which could lead to a disruption in synaptogenesis. This suggests an interesting extension of our work, namely, to couple the trafficking of NMDA receptors with the various extracellular signaling processes that arise during synaptogenesis [1,2]. Indeed, it has been hypothesized that the intermittent cycling of NMDA receptors to the cell surface may allow neurons to sense glutamate released by the axons of other neurons in the vicinity of the given cell as a precursor for synapse formation [7]. In order to study the clustering of NMDA receptors during synapse formation, it would be necessary to include diffusion effects within the plasma membrane (see Fig. 1(b) [3]). It would also be interesting to generalize our model to take into account other forms of protein trafficking prior and during synaptogenesis. For example, it is known that proteins necessary for the assembly of the presynaptic active zone are delivered to immature synapses via exocytosis of intracellular vesicles

[4]. However, in contrast to NMDA within dendrites, these presynaptic vesicles appear to exhibit bidirectional axonal transport prior to synaptogenesis without undergoing periods of exocytosis (endocytosis). Instead, recycling between the surface and interior of the cell is induced by signals from a nascent synapse.

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APPENDIX

In this appendix we present the derivation of the Green's function for the two-state continuum model given by Eqs. (2.3) and (2.4). This is a special case of the more general Green's function derived by Bicout [10] within the context of the Dogterom-Leibler model for the growth and shrinkage of microtubules [17]. Since the analysis applies to any dendritic compartment, we drop the compartmental label n. First, Laplace-transforming equations (2.3) and (2.4) give

$$s\hat{p}(x,s) - p(x,0) = -\beta\hat{p}(x,s) + \alpha\hat{q}(x,s) - v\frac{\partial}{\partial x}\hat{p}(x,s), \tag{A1}$$

$$s\hat{q}(x,s) - q(x,0) = \beta\hat{p}(x,s) - \alpha\hat{q}(x,s). \tag{A2}$$

Assuming the initial condition

$$p(x,0) = \delta(x), \quad q(x) = 0,$$

and rearranging shows that

$$\left[v\frac{\partial}{\partial x} + \gamma(s)\right]\hat{p}_a(x,s) = \left[\delta_{a,1} + \frac{\beta}{(s+\alpha)}\delta_{a,0}\right]\delta(x), \tag{A3}$$

where $\hat{p}_1=\hat{p}$, $\hat{p}_0=\hat{q}$, and

$$\gamma(s) = \frac{s(s+\alpha+\beta)}{s+\alpha} = s + \beta - \frac{\alpha\beta}{s+\alpha}. \tag{A4}$$

Equation (A3) has the solution

$$\hat{p}_a(x,s) = \left[\frac{1}{v}\delta_{a,1} + \frac{\beta}{v(s+\alpha)}\delta_{a,0}\right]e^{-\gamma(s)x/v}\Theta(x), \tag{A5}$$

where Θ is the Heaviside function. We now find the inverse Laplace transform by substituting for $\gamma(s)$ and using the series expansion $\exp[\alpha\beta z/(s+\alpha)]=\sum_{n=0}^{\infty}(n!)^{-1}(\alpha\beta z)^n/(s+\alpha)^n$,

$$p_a(x,t) = \frac{e^{-\beta x/v}}{v}g_a\left(\frac{x}{v},\frac{t-x}{v}\right)\Theta(t-x/v), \tag{A6}$$

with

$$\begin{aligned} g_0(z,t) &= \mathcal{L}^{-1}\left[\sum_{n=0}^{\infty}\frac{\beta}{n!}\frac{(\alpha\beta z)^n}{(s+\alpha)^{n+1}}\right] \\ &= \beta\sum_{n=0}^{\infty}\frac{(\alpha\beta z)^n}{n!}\mathcal{L}^{-1}\left[\frac{1}{(s+\alpha)^{n+1}}\right] \\ &= \beta\sum_{n=0}^{\infty}\frac{(\alpha\beta z)^n}{n!}e^{-t\alpha}\left[\frac{t^n}{n!}\right] = \beta e^{-t\alpha}I_0(2\sqrt{\alpha\beta z t}), \end{aligned} \tag{A7}$$

where I_0 is a modified Bessel function, and

$$\begin{aligned} g_1(z,t) &= \mathcal{L}^{-1}\left[\sum_{n=0}^{\infty}\frac{1}{n!}\frac{(\alpha\beta z)^n}{(s+\alpha)^n}\right] = \sum_{n=0}^{\infty}\frac{(\alpha\beta z)^n}{n!}\mathcal{L}^{-1}\left[\frac{1}{(s+\alpha)^n}\right] \\ &= \delta(t) + \sum_{n=1}^{\infty}\frac{(\alpha\beta z)^n}{n!}e^{-t\alpha}\left[\frac{t^{n-1}}{(n-1)!}\right] \\ &= \delta(t) + e^{-t\alpha}\frac{\partial}{\partial t}I_0(2\sqrt{\alpha\beta z t}) = \delta(t) \\ &\quad + e^{-t\alpha}\sqrt{\frac{\alpha\beta z}{t}}I_1(2\sqrt{\alpha\beta z t}). \end{aligned} \tag{A8}$$

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