Diffusion model of AMPA receptor trafficking in the postsynaptic membrane

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Abstract

AMPA receptors mediate the majority of fast excitatory synaptic transmission in the central nervous system, and evidence suggests that AMPA receptor trafficking regulates synaptic strength, a phenomenon implicated in learning and memory. There are two major mechanisms of AMPA receptor trafficking: exo/endocytotic exchange of surface receptors with intracellular receptor pools, and lateral diffusion of receptors within the postsynaptic density and the extrasynaptic membrane. In this paper we present a mathematical model of these trafficking mechanisms under basal conditions and during the expression of long-term potentiation (LTP) and depression (LTD). Our model differs from previous biophysical models in a number of ways, including the explicit modeling of receptor diffusion in the postsynaptic membrane. We show how our model reproduces a wide range of physiological data, and use this to make predictions regarding possible targets of second-messenger pathways activated during the induction phase of LTP/LTD.
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1 Introduction

Motor control, perception, learning, memory and other characteristic functions of the brain depend upon a neuron’s ability to communicate with other neurons. Understanding neuronal communication has long been the subject of scientific research, beginning in the late nineteenth century with the work of Golgi and Ramón y Cajal (see [1] for a more complete discussion). It was recognized early in these studies that for brain functions to arise from a network of communicating neurons, the network must in some sense be plastic; that is, able to undergo modifications accounting for the experience-dependent adaptation of these functions. However, it took nearly eight decades before researchers demonstrated an activity-dependent plasticity in the mammalian brain [2]. Long-term potentiation (LTP), as it was called, is a lasting increase in the efficacy of synaptic transmission induced by correlations in neural activity. A short time later, a similar plasticity with the opposite effect was discovered, termed long-term depression (LTD) [3]. Since that time, LTP and LTD have been studied extensively in many organisms and in many parts of the nervous system. Various kinds of LTP/LTD have been identified, and many of the mechanisms involved in the induction, expression and maintenance of LTP/LTD have been elucidated (see [4, 5, 6, 7] for reviews). Because LTP/LTD is activity-dependent and ubiquitous at synapses throughout the nervous system, many hypothesize that LTP/LTD represents a prototypical mechanism for learning and memory (see [4, 5, 8, 9] for reviews).

Due in part to the study of LTP/LTD, the synapse is now understood to be a dynamic mosaic of tightly-regulated proteins which are continually synthesized, trafficked, degraded, and interacting with other proteins. In particular, a large body of experimental evidence suggests that the dendritic trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors is responsible for the synaptic changes observed during LTP/LTD (see [10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23] for reviews). AMPA receptors traffick via two major pathways: exo/endocytic exchange of surface receptors with intracellular receptor pools, and lateral diffusion of receptors within the
postsynaptic membrane. Although the precise mechanisms underlying activity-dependent regulation of AMPA receptor trafficking are currently unknown, they are likely to involve the following mechanisms: changes in interactions with scaffolding and transmembrane proteins, changes in the rates of exo/endocytosis, and modifications in the membrane or receptor structure that alter surface transport of receptors. In this paper we present a mathematical model of AMPA receptor trafficking that takes into account all of these mechanisms. Our model consists of a system of differential equations that determines the spatiotemporal dynamics of the synaptic and extrasynaptic concentrations. We analyze these equations to determine the steady-state receptor concentration under basal conditions, and to investigate the time-course of variations in receptor number induced by modifications in one or more model parameters. We show how our model can generate changes in synaptic strength that are consistent with those found in the most studied forms of LTP/LTD, namely, N-methyl-D-aspartate (NMDA) receptor-mediated LTP/LTD. This allows us to identify possible targets of second-messenger pathways that are activated during the induction phase of LTP/LTD.

The paper is organized as follows. We begin with a review of NMDA receptor-mediated LTP/LTD and AMPA receptor trafficking (Section 2). We then present the model (Section 3) and analyze its steady-state behavior under basal conditions (Section 4) and time-dependent behaviors during LTP/LTD (Section 5). We end the paper with a discussion and proposal of future research (Section 6).
2 AMPA receptor trafficking and synaptic plasticity

2.1 Neuronal communication

The axon, a long process emanating from the soma of the message-carrying (presynaptic) neuron, transmits the neuron’s information as a temporal sequence of deviations in its resting membrane potential. These action potentials propagate from the soma to axon terminals at the distal ends of the axon. An axon terminal forms a highly specialized contact site with the message-receiving (postsynaptic) neuron called the synapse. The postsynaptic site of the synapse can be located on a dendrite (another highly branched process of the soma), on the soma itself, or on the axon of the postsynaptic neuron (Figure 1). Excitatory synapses in the CNS are almost always formed on a filopodial protrusions of the dendrite called dendritic spines.

The synapse is the locale of neuron-to-neuron communication. When an action potential reaches an axon terminal, the accompanying change in the terminal’s membrane potential opens voltage-gated calcium channels spanning the membrane. The increased intracellular Ca^{2+} concentration initiates second-messenger pathways that cause vesicles containing neurotransmitters to fuse with a specialized area of the presynaptic membrane called the active zone. The fused vesicles secrete their contents into the synaptic cleft, the extracellular space between the pre- and postsynaptic membranes. The neurotransmitter diffuses through the cleft and binds with a variety of receptors embedded in the postsynaptic membrane (Figure 2). If the synapse is excitatory – that is, if it acts to propagate the action potential – then this binding affects a depolarization of the postsynaptic membrane. For example, the binding of glutamate (the major excitatory neurotransmitter in the CNS) to the ionotropic AMPA receptor begins a rapid influx of sodium ions through the receptor pore, accounting for most of the depolarization. This synaptic potential then diffuses to the soma of the postsynaptic neuron, where it integrates with synaptic potentials from other synapses until a sufficiently depolarized axon trigger zone, located at
Figure 1: Schematic of a prototypical neuron, demonstrating the soma, axon, dendrites and synapses. (Adapted from [1])
Figure 2: Schematic of synaptic transmission. The arrival of an action potential at an axon terminal causes a presynaptic release of neurotransmitter which binds to selective receptor channels on the postsynaptic membrane. These ligand- and voltage-gated channels open and allow an influx of ions (typically Na\(^+\)), creating the synaptic potential. (Adapted from [1])

the somatic base of the axon process, produces an action potential that starts again the communication pathway.

2.2 NMDA receptor-mediated LTP/LTD

A remarkable property of the synapse is its ability to regulate the efficacy of its own synaptic transmission, a phenomenon called synaptic plasticity. As mentioned above, LTP/LTD are well-studied, prototypical forms of synaptic plasticity. Typical recordings made during LTP/LTD experiments are shown in Figure 3. In slice preparations (e.g., from the CA1 region or dentate gyrus of the hippocampus) LTP is induced either by delivering a brief tetanic stimulus (e.g., 100 Hz for 1 s) to the postsynaptic neuron, or pairing stimulus delivery with a large membrane depolarization. LTD is induced either by delivering a low-frequency stimulus for many minutes (e.g., 1 Hz for 15 min) or pairing stimulus delivery with a small membrane depolarization. Both LTP/LTD can be divided
Figure 3: Typical LTP/LTD recordings from populations of synapses (top) and single synapses (bottom). LTP is characterized by a lasting (> 1 hr) increase in the amplitude of excitatory postsynaptic potentials (EPSPs), while LTD is characterized by a lasting decrease in EPSPs. The rapid depression of the single-synapse LTD recordings is likely due to a LTD-related phenomenon called **depotentiation** (see Section 6 under the heading “Discrete synaptic states” for a discussion of depotentiation). (Top left adapted from [4], top right adapted from [24], bottom adapted from [27])
into two phases. *Early-phase* LTP/LTD is characterized by a change in the amplitude of synaptic potentials lasting an hour after stimulus delivery, the amplitude increasing during LTP and decreasing during LTD. These early-phase changes are due mainly to variations in the number and function of postsynaptic AMPA receptors. In *late-phase* LTP/LTD, the change in synaptic potential amplitude lasts anywhere from a few hours to the entire lifetime of the synapse and requires new protein synthesis and gene transcription (see [28, 7] for reviews). Because of its dependence on AMPA receptor trafficking, this paper is mainly concerned with the early-phase of LTP/LTD. Also, the term weight of a synapse is often used to denote the amplitude of the synaptic potential, and one speaks of LTP and LTD as up- and down-regulating the synaptic weight, respectively. We will use this convention throughout the rest of the paper.

A ubiquitous form of LTP/LTD at CNS excitatory synapses depends upon the activation of N-methyl-D-aspartate (NMDA) receptors (Figure 4). NMDA receptors mediate

![NMDA receptor schematic](image)

*Figure 4: Schematic of an NMDA receptor, depicting the glutamate and Mg2+ gates, as well as a variety of function modulators. (Adapted from [29])*
the influx of Ca\textsuperscript{2+} into the dendritic spine, and the spatiotemporal pattern of this intracellular Ca\textsuperscript{2+} signal triggers second-messenger pathways within the neuron that affect the up- or down-regulation of the synaptic weight. Like AMPA receptors, NMDA receptors require glutamate to allow ion flow. Unlike AMPA receptors, however, the NMDA receptor possesses a voltage-sensitive magnesium binding site located within its pore. At resting membrane potential, Mg\textsuperscript{2+} binds the site with high affinity, blocking all ion flow through the receptor. However, as the membrane potential depolarizes, the Mg\textsuperscript{2+} site releases the bound ion, allowing Ca\textsuperscript{2+} to flow if the receptor has already bound glutamate. These two Ca\textsuperscript{2+} gates make NMDA receptors the primary mechanism for indicating correlations in pre- and postsynaptic activity to the synapse: an NMDA receptor detects the coincidence of glutamate release from the presynaptic terminal and the accompanying depolarization of the postsynaptic membrane, and communicates this coincidence to the postsynaptic neuron through increased levels of intracellular Ca\textsuperscript{2+} concentration.

Throughout the rest of the paper, when we refer to LTP/LTD we will have NMDA receptor-mediated LTP/LTD at CNS excitatory synapses in mind. It should be noted, however, that many varieties of LTP/LTD have been identified at various types of synapses throughout the nervous system, and that the modifications affecting LTP/LTD can be both pre- and postsynaptic [7].

2.3 AMPA receptors

AMPA receptors are a type of glutamate receptor found primarily in the CNS. Glutamate receptors can be divided into two functional categories: metabotropic, which mediate their effects via coupling to G-protein second messenger systems, and ionotropic, which are ligand-gated cation channels. Ionotropic glutamate receptors can be further separated into three pharmacological groups: AMPA, NMDA, and kainate receptors, named for synthetic agonists which readily activate the receptors (see [30, 31] for reviews). AMPA receptors mediate the fast Na\textsuperscript{+} influx that accounts for the majority of synaptic transmission at
CNS excitatory synapses. AMPA receptors primarily gate $\text{Na}^+$ in preference to $\text{Ca}^{2+}$, due to subunit composition [30], and in preference to $\text{K}^+$, due perhaps to their large pore size [32]. Topologically, AMPA receptors are hetero-tetramers of four subunits named GluR1 to GluR4 (Figure 5). Each subunit is comprised of an extracellular N-terminal domain, four hydrophobic regions named TM1 to TM4, and an intracellular C-terminal domain. TM2 is a cytosolic hairpin loop which, together with the TM2 region of the other three subunits, forms the cation pore. The C-terminal domain contains a number of phosphorylation sites and conserved sequences that interact with other intracellular proteins (see [15, 20, 22] for reviews). The subunit composition of an AMPA receptor determines the manner in which it is trafficked, both under basal conditions and during the expression of LTP/LTD. This difference depends on whether the AMPA receptor contains a subunit with a long C-terminal domain (typically GluR1 or GluR4) or is comprised only of subunits with short C-terminal domains (typically GluR2 and GluR3, see Figure 6). The majority of AMPA receptors at mature CNS excitatory synapses are either GluR1/2 or GluR2/3 heteromers [30], and hence these two receptor classes play

![Figure 5: Schematic of AMPA receptor subunit (GluR) topology, demonstrating the N- and C-terminal domains, the four regions TM1-4, ligand binding domain, PDZ interaction domains, and phosphorylation sites. (Adapted from [22])](image)
different trafficking roles under basal and activity-dependent conditions.

2.4 AMPA receptor trafficking

In dendritic spines there is an electron-dense thickening of the postsynaptic cytoskeleton just below the membrane that is directly apposed to the presynaptic active zone called the postsynaptic density, or PSD (see [33, 34, 35, 10] for reviews). The PSD is a subsynaptic scaffold that localizes and organizes the various receptors, ion channels, kinases, phosphatases and signalling molecules present in the dendritic spine. Many of the proteins found in the PSD contain interaction motifs termed PDZ domains (named for the first three proteins in which the domain was observed: PSD95, discs large, and zona occludens 1). Such domains allow a wide range of protein-to-protein interactions, giving rise to the dynamics of the postsynaptic membrane, including AMPA receptor trafficking.

A schematic of AMPA receptor trafficking at a dendritic spine is shown in Figure
7. Receptors in the extrasynaptic membrane (ESM) of the spine diffuse freely, possibly

Figure 7: Schematic of AMPA receptor trafficking at a dendritic spine. Receptors stored in intracellular pools are continually exchanged with surface receptors through exo/endocytosis (EXO/END) and sorted for degradation (DEG). Surface receptors diffuse in the dendritic membrane and can be immobilized at the PSD through interactions with scaffolding proteins. as part of large receptor-scaffold complexes [18]. Due to the high density of scaffolding proteins constituting the PSD, the PSD acts as a confinement domain for surface AMPA receptors: the boundary of the PSD and ESM acts as a barrier to receptor entry/exit, and receptor diffusion within the PSD proceeds in a highly obstructed manner, with receptors often binding to scaffolding proteins. [36, 37, 38, 23] (see Figure 8). Estimates for the diffusivity range from 0.01 to 0.5µm²/sec [36, 37, 38, 39, 40]. The narrow, highly curved spine neck also impedes receptor diffusion, slowing the exchange of receptors between the spine head and dendritic cable [40]. Surface receptors are continually exchanged with intracellular receptor pools through exo- and endocytosis, and are either reinserted into the membrane or sorted to lysosomes for degradation [41, 42, 43, 44, 45, 39]. Passafaro et al. [43] estimate exocytosis into the PSD and ESM to have a time constant of 10 min and 30 min, respectively; however, data obtained by Adesnik et al. [39] using different methods
Figure 8: AMPA receptor diffusion. The mean square displacement (MSD) of extrasynaptic receptors (upper right) is linear in time, indicating free (Brownian) diffusion, while the MSD of synaptic receptors (lower right) is sublinear, indicating confined diffusion. (Adapted from [37])

estimates the PSD exocytic time constant to be much longer, on the order of many hours. Ehlers [42] found that the rate of endocytosis from the ESM is comparable to Passafaro et al.’s rate of exocytosis into the PSD. Notice that there is no endocytosis from the PSD [44], consistent with the emerging view that during constitutive recycling receptors translocate from the PSD to the ESM where they are endocytosed. The intracellular pool is probably large and may represent as much as 80%-90% of the total number of AMPA receptors at hippocampal neurons [20, 39].

**Basal trafficking.** Under basal conditions, AMPA receptor concentration in the postsynaptic membrane is high at the PSD, drops off dramatically at the boundary of the PSD, and remains low throughout the ESM [46, 47, 37, 48] (Figure 9). Estimates of receptor concentrations within the PSD range from 100 to 1000 receptors µm$^{-2}$, whereas within the ESM they range from 1 to 20 receptors µm$^{-2}$. The total number of receptors in the PSD depends on the size of the PSD and can vary from 1 to 200. The majority of AMPA
receptors at the PSD are GluR2/3 heteromers, due to an activity-independent exchange of synaptic AMPA receptors with GluR2/3 heteromers. This basal turnover creates a steady flux of receptors along the postsynaptic membrane from the PSD to the perisynaptic region where they enter the endocytic pathway. The PDZ domain-containing protein N-ethylmaleimide-sensitive factor (NSF), an ATPase involved in membrane-fusion events, is thought to mediate this exchange [13, 20] (although see [22]). The GluR2/3 heteromers are stabilized in the PSD through interactions with multi-PDZ-domain-containing glutamate-receptor-interacting proteins (GRIPs) and AMPA-receptor-binding proteins (ABPs), and are clustered together through interactions with neuronal-activity-regulated pentraxin (NARP) [13, 15]. While the association with GRIP/ABP is specifically with GluR2/3 heteromers, NARP interacts with all AMPA receptor subunits.

A few experiments give insight into the balance of the basal fluxes produced by exo/endocytosis and the mobility of receptors. Luscher et al. [41] blocked each of exo/endocytosis pharmacologically and recorded the accompanying change in field potentials (Figure 10). Blocking exocytosis by loading synapses with BoTox caused an ≈50% reduction in the population EPSPs over 10-20 min, while blocking endocytosis by loading synapses with the peptide D15 produced an ≈50% increase in the population EPSPs over
the same time period. With regards to mobility, Groc et al. [38] and Ashby et al. [40] both determined, by single-particle tracking, the diffusivity of mobile synaptic receptors to be $\approx 0.01 \mu \text{m}^2/\text{sec}$, and that the fraction of mobile AMPA receptors within the PSD of mature dendritic spines is approximately half of all the receptors found there. Thus even under basal conditions, AMPA receptor concentrations are maintained by a dynamic balance of exo/endocytosis, diffusion, and immobilization by scaffolding proteins.

**LTP/LTD trafficking.** By definition, the induction of NMDA receptor-mediated LTP begins with the influx of $\text{Ca}^{2+}$ into the dendritic spine through activated NMDA receptors. Although this rise in $\text{Ca}^{2+}$ is essential for inducing LTP, little is known about the spatiotemporal properties of the $\text{Ca}^{2+}$ signal required for induction [6, 7]. Also, though it is known that the increased levels of $\text{Ca}^{2+}$ concentration activate second-messenger pathways within the neuron, there is little consensus on which pathways are involved [50]. It is almost certain, however, that calcium/calmodulin-dependent protein kinase II (CaMKII) is required for NMDA receptor-mediated LTP [51]. It is thought that CaMKII acts as a molecular switch for the expression of LTP which is activated by the large rise in intracellular $\text{Ca}^{2+}$ accompanying the induction of LTP. [52, 53]. The activation of CaMKII by $\text{Ca}^{2+}$ increases the rate of exocytosis of GluR1/2 heteromers into the ESM. Although the
exact mechanism is unknown, it is thought that CaMKII phosphorylates synapse-associate protein 97 (SAP-97), the only PDZ-domain-containing protein known to bind with GluR1 and which has been implicated in the delivery of GluR1/2 heteromers to the postsynaptic membrane due to its interactions with the motor protein myosin-VI [54, 55, 56, 57]. Also, stargazin and other transmembrane AMPA receptor regulatory proteins (TARPs) play a crucial role in the membrane expression of GluR1/2 heteromers and their incorporation into the PSD [58, 59, 60]. Interestingly, stargazin binds with the PDZ-domain-containing protein PSD-95, a major scaffolding protein of the PSD, and evidence suggests that the concentration of PSD-95 at the PSD directly determines the number of AMPA receptors found there [61, 49]. It is hypothesized that the binding of PSD-95 to the actin cytoskeleton that accompanies the translocation of GluR1/2 heteromers into the PSD provides additional binding sites for constitutively recycling GluR2/3 heteromers, thereby maintaining the increase in AMPA receptor number [13, 14, 16, 17, 18].

As in the case of LTP, NMDA receptor-mediated LTD is induced by a rise in intracellular calcium levels. Although it is not well understood, the spatiotemporal properties of the Ca\(^{2+}\) signal determine whether LTP or LTD is induced: LTP is induced by a large, fast increase of intracellular Ca\(^{2+}\) concentration in the dendritic spine while LTD is induced by a moderate, slow increase which may be accompanied by Ca\(^{2+}\) release from intracellular stores [62, 7]. Just as LTP is associated with an increase in the number of synaptic AMPA receptors due to the influx of receptors from the ESM, LTD involves a loss of receptors from the PSD due to modifications in constitutive recycling [63, 64, 65, 66, 67]. A possible trigger for LTD expression is the activation of a phosphatase cascade involving calcineurin and protein phosphatase 1 (PP1) [68, 69]. Though the mechanisms underlying LTD expression are not as well understood as those for LTP, some possible candidates have been identified. First, induction of LTD triggers the phosphorylation of constitutive GluR2/3 heteromers by activated PKC\(\alpha\) [70, 71, 72]. This disrupts their interactions with the stabilizing GRIP/ABP complexes and allows for association with PICK1. PICK1 medi-
ates the loss of AMPA receptors at the PSD, as the overexpression of PICK1 at synapses is correlated with a decrease in membrane expression of AMPA receptors [72]. Second, the clathrin adaptor protein AP2 is known to bind with AMPA receptors at a site that overlaps with the NSF binding site, the protein implicated in the constitutive recycling of GluR2/3 heteromers [73]. It is thought that an LTD induction trigger blocks NSF binding and promotes AP2 binding. In combination with the mechanism above, the free AMPA receptor with bound AP2 is recruited to perisynaptic clathrin-coated pits and endocytosed [67, 11, 44]. Third, there exists some indirect experimental evidence for the removal of scaffolding proteins from the PSD during LTD, namely, that NMDA receptor activation can lead to the ubiquitination and subsequent degradation of the scaffolding protein PSD-95 [74]. The removal of a scaffolding protein releases the associated bound receptor, which can then diffuse out of the PSD and be internalized through endocytosis.
3 The model

In order to investigate the role of AMPA receptor trafficking in synaptic plasticity, we construct a simplified two-compartment model of a dendritic spine’s surface membrane, in which the spine is treated as a uniform cylinder of radius $r_0$ and length $z_0$ with one end open and the other closed (see Figure 11). The first compartment represents the PSD region of the spine head, and is modeled by the flat disc at the sealed end of the cylinder. The second compartment represents the ESM of the remaining spine head and neck, and is modeled by the curved surface of the cylinder. The circular boundary at the open end of the cylinder represents the junction of the spine with the surface of the dendritic shaft. Surface receptors can flow in both directions across this boundary, with the net flux depending on the concentration of surface receptors relative to some background level. Our model simplifies the geometry of a dendritic spine by ignoring the narrowing of the spine at the spine neck. This could be modeled by taking a cylinder with a smoothly

![Figure 11: Model geometry. (Left) Simplified two-compartment model of a dendritic spine. The PSD is modeled as a disk at the end of a cylinder, while the extrasynaptic membrane (ESM) of the spine head is modeled as the curved surface of the cylinder. The open end of the cylinder represents the junction of the spine head with the dendritic shaft. (Right) Cross-section through cylindrical model of spine showing the various trafficking parameters. Rates of binding/unbinding, hopping, and endocytosis depend on receptor type. Only type II receptors (GluR2/3) undergo exocytosis in the PSD and only type I receptors (GluR1/2) undergo exocytosis in the ESM.](image-url)
varying diameter, but it would considerably complicate the analysis of surface diffusion
due to associated curvature effects [75]. Here we follow a simpler approach by introducing
a large diffusive impedance $\Omega$ at the boundary between the spine and dendritic shaft.
Given the simplified spine geometry, the concentration of mobile receptors within the
PSD is taken to be radially symmetric. That is, if $r$ denotes the radial distance from the
center of the PSD, then the concentration of mobile receptors within the PSD is described
by a function $P(r)$ with $0 \leq r \leq r_0$. Similarly, the mobile receptor concentration within
the ESM is taken to be axially symmetric. That is, if $z$ represents the axial distance
along the cylinder from the PSD, then the concentration is given by a function $R(z)$
with $0 \leq z \leq z_0$. Based on typical sizes of the PSD and spine we take $r_0 = 0.2\mu m$ and
$z_0 = 1\mu m$ [34].

We assume that AMPA receptors diffuse freely in the ESM with diffusivity $D_z$. We
distinguish between receptors that move freely within the PSD and those that are trapped
by scaffolding proteins. We assume that the movement of free receptors can be character-
ized by an effective diffusivity $D_r$ (see Section 2.4). Transitions between free and bound
receptors are described according to the first-order kinetic scheme

$$P + L \xrightleftharpoons[\beta]{\alpha} Q$$

where $L$ denotes the concentration of scaffolding proteins within the PSD, $Q$ is the con-
centration of bound receptors, $\alpha$ is the binding or trapping rate and $\beta$ is the release rate.
One could also consider more complicated trapping models, involving different types of
scaffolding proteins, and the effects of receptor clustering (see Section 6). In order to
model the confinement of diffusing particles within the PSD, we treat the circular bound-
ary between the PSD and ESM compartments as a potential barrier over which receptors
must hop in order to enter or exit the PSD. For simplicity, the net flux across the boundary
is taken to be proportional to the difference in concentrations on either side of the barrier,
with the constant of proportionality given by a hopping rate $h$. An alternative model of
confinement is to assume that the boundary between the PSD and ESM is impermeable
except for small openings within the boundary through which receptors can diffuse [76].

When modeling exo/endocytosis, we recall that there are at least two separate sources of intracellular AMPA receptors: GluR1/2 heteromers inserted into the ESM during LTP, and GluR2/3 heteromers inserted into the PSD during constitutive recycling. Since the expression of LTP and LTD is thought to involve changes in the trafficking of GluR1/2 and GluR2/3 respectively, it is important to distinguish explicitly between these two receptor types. For ease of notation we denote GluR1/2 heteromers as type I and GluR2/3 heteromers as type II. We then decompose the free receptor concentrations according to

\[ P = P_I + P_{II} \quad \text{and} \quad R = R_I + R_{II}. \]

Similarly, the bound receptor concentration within the PSD is decomposed as \( Q = Q_I + Q_{II}. \) We allow for the possibility that the first-order kinetics of binding to scaffolding proteins may differ for the two receptor types, as, may the hopping rate across the PSD-ESM boundary. Thus we have two distinct sets of parameters \( \{h_I, \alpha_I, \beta_I\} \) and \( \{h_{II}, \alpha_{II}, \beta_{II}\}. \) We denote the rate of exocytosis of type I receptors into the ESM by \( \sigma_I \) and the corresponding rate of exocytosis of type II receptors into the PSD by \( \sigma_{II}. \) At basal levels both \( \sigma_I \) and \( \sigma_{II} \) can be treated as approximately constant, since the intracellular pools contain a relatively large number of receptors compared to that at the surface (see Section 2.4). However, during LTP, the rapid insertion of GluR1/2 into the ESM through exocytosis will deplete the corresponding intracellular pool so that \( \sigma_I \) can no longer be treated as time-independent (see Section 5.1). We further assume that both receptor types undergo endocytosis from the ESM at some rate \( k_j, j = I, II. \)

We analyze our model in terms of the corresponding set of differential equations describing the time evolution of the receptor concentrations in the PSD and ESM (see Section 3.1). Solutions of the model equations are used to investigate how receptor trafficking depends on the various biophysical parameters, including the diffusivities \( D_x \) and \( D_z \) in the PSD and ESM, the rates of exo/endocytosis \( \sigma_j \) and \( k_j, \) the rates of binding/unbinding to scaffolding proteins \( \alpha_j \) and \( \beta_j, \) and the number of binding sites \( L \) within the PSD. These parameters are possible targets of second-messenger pathways initiated by a rise
Table 1: Basal parameter values. *The nontrafficking parameters do not have particular type I and II values.

in intracellular Ca\textsuperscript{2+} during the induction phase of LTP/LTD. A basic assumption of our modeling approach is that there is a separation of time-scales between the activation of the signaling pathways by the postsynaptic calcium signal during induction (seconds) and the subsequent expression of LTP/LTD (minutes). Under such an assumption, it is possible to study the mechanisms underlying the expression of LTP/LTD independently of the particular signaling pathways involved in induction.

We assume throughout that $D_r$, $\sigma_I$, $\alpha_j$, $\beta_j$ and $L$ are spatially uniform within the PSD and $D_z$, $k_j$ and $\sigma_{II}$ are spatially uniform within the ESM. The parameter values chosen for receptor trafficking under basal conditions are listed in Table 1. As some of the model parameters have yet to be determined experimentally (e.g., the rate at which AMPA receptors bind to and are released from scaffolding proteins), we select values for these parameters that produces results consistent with the known experimental data.
Our choice for the rate of exocytosis is based on the work of Passafaro et al. [35], which suggests time constants for exocytosis of $\approx 10-30$ min. Given a basal rate of exocytosis $\sigma \approx \kappa S$, where $S$ is the steady-state number of receptors in the intracellular pool, we take $\kappa$ to be the reciprocal of the time constant. For GluR2/3 receptors, we choose the rate of endocytosis approximately to balance the flux due to exocytosis, which yields the constitutive recycling of GluR2/3 heteromers at the dendritic spine. We take the rate of endocytosis to be slower for GluR1/2 receptors, as this allows our extrasynaptic receptor concentrations to approximate those observed experimentally [47]. Both of these endocytic rates are not unlike those suggested by Ehlers [42]. As was mentioned above, both Groc et al. [38] and Ashby et al. [40] showed that diffusion of AMPA receptors at the synapse is fast compared to the spatial scale of the dendritic spine, and approximately half of all synaptic receptors are mobile. Given our choices of exo/endocytic rates, we cannot treat the membrane at the junction between the PSD and ESM as continuous, as this does not account for this data. We therefore follow Triller and Choquet [23] and Holcman and Schuss [76] in treating this junction as a potential barrier to receptor movement. We choose the hopping rate $h$ of receptors across this barrier so that, with diffusivities consistent with the data of Groc et al. and Ashby et al., the model predicts a large number of free receptors in the PSD. Since GluR2/3 receptors are inserted directly into the PSD, the majority of basal free receptors found in the PSD in our model are of this type. We then select the basal number of active binding sites to approximately match the number of free receptors, and choose basal binding and release rates so that nearly all of the binding sites are filled by GluR2/3 receptors, and they are consistent with other known systems [77]. Note that taking the binding sites to be unsaturated, that is, to have a significant fraction of free binding sites, would require unrealistically low binding affinities. This, in turn, makes it difficult to match the range of experimental data presented below.

It is important to note that recently there have been a number of biophysically moti-
vated models of LTP/LTD [78, 79, 80, 81, 82, 83]. However, these have tended to focus on the role of Ca\(^{2+}\) as an induction signal for bidirectional synaptic plasticity, rather than on the role of AMPA receptor trafficking in the expression of synaptic plasticity.

### 3.1 Model equations

The free and bound receptor concentrations in the synaptic membrane (0 ≤ r < r_0) satisfy the equations

\[
\frac{\partial P_I}{\partial t} = \frac{D_r}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P_I}{\partial r} \right) - \alpha_I (L - Q_I - Q_{II}) P_I + \beta_I Q_I, \tag{1}
\]

\[
\frac{\partial P_{II}}{\partial t} = \frac{D_r}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P_{II}}{\partial r} \right) + \frac{\sigma_{II}}{A_r} - \alpha_{II} (L - Q_I - Q_{II}) P_{II} + \beta_{II} Q_{II}, \tag{2}
\]

and

\[
\frac{\partial Q_I}{\partial t} = \alpha_I (L - Q_I - Q_{II}) P_I - \beta_I Q_I, \tag{3}
\]

\[
\frac{\partial Q_{II}}{\partial t} = \alpha_{II} (L - Q_I - Q_{II}) P_{II} - \beta_{II} Q_{II}. \tag{4}
\]

The first term on the right-hand side of equations (1,2) represents radial diffusion in the PSD with diffusivity \(D_r\), and the last two terms represent binding and unbinding to a uniform concentration of active traps \(L\) with rates \(\alpha\) and \(\beta\), respectively, dependent on receptor type. The type II receptors also undergo exocytosis within the PSD at an insertion rate \(\sigma_{II}\), and \(A_r = \pi r_0^2\) is the area of the PSD. The rate of exocytosis satisfies \(\sigma_{II} = \kappa_{II} (1 - f) S_{II}\), where \(S_{II}\) is the number of type II receptors in the intracellular store, \(1 - f\) is the fraction of intracellular receptors recycled to the surface (rather than degraded), and \(\kappa_{II}\) is the insertion rate per receptor. \(S_{II}\) satisfies the first-order equation

\[
\frac{dS_{II}}{dt} = k_{II} N_{z,II} + \delta_{II} - [(1 - f) \kappa_{II} + f \kappa_{deg}] S_{II} \tag{5}
\]

where \(\delta_{II}\) is the net rate of receptor synthesis, \(\kappa_{deg}\) is the rate of receptor degradation, and \(N_{z,II}\) is the total number of type II receptors in the ESM (see below). We assume that
the intracellular pool of GluR2/3 receptors is sufficiently large and the rate of receptor insertion is sufficiently slow so that the depletion of the pool due to exocytosis can be neglected, that is, $\sigma_{II}$ can be treated as a constant.

The receptor concentrations in the ESM ($0 < z < z_0$) satisfy the equations

$$\frac{\partial R_I}{\partial t} = D_z \frac{\partial^2 R_I}{\partial z^2} + \frac{\sigma_I}{A_z} - k_I R_I,$$

$$\frac{\partial R_{II}}{\partial t} = D_z \frac{\partial^2 R_{II}}{\partial z^2} - k_{II} R_{II}.$$

The first term on the right-hand side of equations (6,7) represents axial diffusion in the ESM with diffusivity $D_z$, and the last term represents endocytosis at a rate $k_j$. The type I receptors also undergo exocytosis at a rate $\sigma_I$. The total surface area of the ESM is denoted by $A_z = 2\pi r_0 z_0$. The rate of exocytosis is given by $\sigma_I = \kappa_I S_I$ where $S_I$ is the number of type I receptors in the associated intracellular store and $\kappa_I$ is the insertion rate per receptor. $S_I$ evolves according to the first-order equation

$$\frac{dS_I}{dt} = -\kappa_I S_I + \delta_I,$$

where $\delta_I$ is the net rate of receptor synthesis.

The above equations have to be supplemented by appropriate boundary conditions. First, for each receptor type we assume that the flux across the circular boundary between the PSD and ESM is continuous, and depends upon the difference in concentrations across the boundary:

$$J_{r,j}(r_0) = J_{z,j}(0) = h_j [P_j(r_0) - R_j(0)]$$

for $j = I, II$, with $h_j$ a hopping rate. The receptor fluxes are defined according to

$$J_r = -D_r \frac{\partial P}{\partial r}, \quad J_z = -D_z \frac{\partial R}{\partial z}.$$

Here $J_r$ denotes the flux within the PSD with $2\pi r J_r(r)$ corresponding to the rate at which receptors cross a circle of radius $r$ concentric with the PSD. Similarly, $J_z$ denotes the flux within the ESM with $2\pi r_0 J_z(z)$ corresponding to the rate at which receptors cross a circle
of radius $r_0$ at an axial distance $z$ from the PSD. We also impose a mixed boundary condition on the outer border of the ESM,

$$\Omega J_{z,j}(z_0) = R_j(z_0) - R_{j,0}$$

for $j = I, II$, where $R_{j,0}$ is the background concentration of receptor type $j$ and $\Omega$ is a diffusive impedance. Finally, given the receptor concentrations $P_j$, $Q_j$ and $R_j$, the total number of AMPA receptors in the PSD is $N_r = N_{r,I} + N_{r,II}$, with

$$N_{r,j} = 2\pi \int_0^{r_0} r (P_j(r) + Q_j(r)) dr$$

and the total number of AMPA receptors in the ESM is $N_z = N_{z,I} + N_{z,II}$, with

$$N_{z,j} = 2\pi r_0 \int_0^{z_0} R_j(z) dz$$

### 3.2 Model extension during LTD

We describe the extension of our model used in the study of LTD (see Section 5.2). As in the case of LTP, the precise molecular mechanisms underlying the regulation of receptor trafficking during LTD are still being determined. Nevertheless, we can use our diffusion model to explore how such changes in receptor trafficking combine with lateral membrane diffusion to generate responses that are consistent with those observed during LTD. In order to proceed, we extend our basic model by assuming that bound GluR2/3 receptors within the PSD exist in two distinct states with concentrations $Q_{II}$ and $Q_{II}^*$, corresponding to association with GRIP/ABP and PICK1, respectively (see Section 2.4). Transitions between the two states are described according to the first-order kinetic scheme

$$Q_{II} \xrightarrow{\mu} Q_{II}^* \xrightarrow{\nu} Q_{II}.$$  

Receptors in the $Q_{II}$ state behave as in the previous model, whereas those in the $Q_{II}^*$ state untether from binding sites at a rate $\beta^*$, and then diffuse to the ESM where they are endocytosed. Suppose that under basal conditions the transition rate $\mu$ from $Q_{II}$ to
$Q_{II}$ is negligible so that $Q_{II}^* = 0$. We now assume that during the induction phase of LTD $\mu$ rapidly increases, leading to the conversion of some bound receptors from $Q_{II}$ to $Q_{II}^*$, and a corresponding reduction in the number of receptors in the PSD. However, on its own, this mechanism would not maintain LTD once the low frequency stimulus is removed. For there is currently no evidence for a bistable switch analogous to CaMKII that would allow levels of phosphorylation to persist. Therefore, $Q_{II}^*$ would convert back to $Q_{II}$ and the synapse would recover. In order to have a persistent reduction in synaptic strength, we assume that as receptors untether from binding sites, these sites are removed at some rate $\gamma$. Writing the concentration of free receptors in the PSD as $P_{II}$ and $P_{II}^*$, we have the following extended system of equations,

$$\begin{align*}
\frac{\partial P_{I}}{\partial t} &= \frac{D_{r}}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P_{I}}{\partial r} \right) - \alpha_{I}(L - Q_{I} - Q_{II} - Q_{II}^*)P_{I} + \beta_{I}Q_{I}, \\
\frac{\partial P_{II}}{\partial t} &= \frac{D_{r}}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P_{II}}{\partial r} \right) + \frac{\sigma_{II}}{A_{r}} - \alpha_{II}(L - Q_{I} - Q_{II} - Q_{II}^*)P_{II} + \beta_{II}Q_{II}, \\
\frac{\partial P_{II}^*}{\partial t} &= \frac{D_{r}}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P_{II}^*}{\partial r} \right) + \beta_{II}^*Q_{II}^*, \\
\frac{\partial Q_{I}}{\partial t} &= \alpha_{I}(L - Q_{I} - Q_{II} - Q_{II}^*)P_{I} - \beta_{I}Q_{I}, \\
\frac{\partial Q_{II}}{\partial t} &= \alpha_{II}(L - Q_{I} - Q_{II} - Q_{II}^*)P_{II} - \beta_{II}Q_{II} - \mu Q_{II} + \nu Q_{II}^*, \\
\frac{\partial Q_{II}^*}{\partial t} &= -\beta_{II}^*Q_{II}^* + \mu Q_{II} - \nu Q_{II}^*, \\
\frac{\partial L}{\partial t} &= -\gamma(L - Q_{I} - Q_{II} - Q_{II}^*). \tag{20}
\end{align*}$$

and

3.3 Description of numerics

All figures in this paper were produced using MATLAB. Steady-state figures were produced by plotting their analytic formulations. Figures containing time-evolution data
were produced using a finite area numerical approximation of our model partial differential equations. A finite area method was chosen to conserve surface receptors, as the paradigm of this method computes the total flux into and out of an area, rather than computing the change in concentration at a single point. For updating, we employed the standard backward Euler method, discretizing the diffusion operator and time derivative in the standard way.

Backward Euler is known to be second-order accurate in space. Our finite area method requires the computation of flux at the junctions in our model (at $r = r_0$ and $z = z_0$), yet the method does not have a data point at any junction, since the data points are always interior to their representative areas and the junctions are always area boundaries. However, we can still maintain second-order accuracy at these junctions in the following way. At $r = r_0$, we use a weighted harmonic mean of the diffusion coefficients $D_r$ and $D_z$ as an effective diffusion coefficient $D_{eff}$; i.e.,

$$D_{eff} = \frac{2D_r D_z (\Delta r + \Delta z)}{D_r \Delta z + D_z \Delta r}$$

where $\Delta r$ and $\Delta z$ are the spatial step lengths in the disk and on the cylinder, respectively.

It is well-known that this choice of effective diffusion coefficient for spatially inhomogeneous diffusion coefficients preserves second-order accuracy. Because the surface receptor concentration may be discontinuous at $r = r_0$, we compute the flux there by extrapolating the concentrations in the PSD and ESM simultaneously, as follows. Let $P_K$ be the last point in our discretization of $P$ (so that the boundary of the area containing $P_K$ includes the junction of the PSD and the ESM) and let $R_1$ be the first point in our discretization of $R$ (so that the boundary of the area containing $R_1$ includes the same junction). A discretization of the boundary conditions (9) yields the following system of equations for $P_{K+1}$ and $R_0$:

$$-D_{eff} \frac{P_{K+1} - P_K}{\Delta r} = h \left( \frac{P_{K+1} + P_K}{2} - \frac{R_1 + R_0}{2} \right)$$

$$-D_{eff} \frac{R_1 - R_0}{\Delta z} = h \left( \frac{P_{K+1} + P_K}{2} - \frac{R_1 + R_0}{2} \right)$$
The left-hand sides of these equations represent discretizations of the flux at \( r = r_0 \) (equivalently, at \( z = 0 \)), and the values \((P_{K+1} + P_K)/2\) and \((R_1 + R_0)/2\) are midpoint interpolations of the concentrations \( P(r_0) \) and \( R(0) \), respectively, using the points \( P_{K+1} \) and \( R_0 \) that we are attempting to extrapolate. The solution to these equations is

\[
P_{K+1} = \frac{\theta_r \theta_z + \theta_r - \theta_z}{\theta_r \theta_z + \theta_r + \theta_z} P_K + \frac{2}{\theta_r \theta_z + \theta_r + \theta_z} R_1
\]

\[
R_0 = \frac{2}{\theta_r \theta_z + \theta_r + \theta_z} P_K + \frac{\theta_r \theta_z - \theta_r + \theta_z}{\theta_r \theta_z + \theta_r + \theta_z} R_1
\]

where \( \theta_r = 2D_r/(h \Delta r) \) and \( \theta_z = 2D_z/(h \Delta z) \). We can now compute the discretized flux:

\[
-D_{\text{eff}} \frac{P_{K+1} - P_K}{\Delta r} = -D_{\text{eff}} \frac{R_1 - R_0}{\Delta z} = \frac{P_K - R_1}{1/h + (\Delta r + \Delta z)/(2D_{\text{eff}})}
\]

Notice that this approximation is independent of the extrapolated values \( P_{K+1} \) and \( R_0 \). This method of computing the flux inherits second-order accuracy from the midpoint interpolation used above.

The flux at \( z = z_0 \) was computed in a similar way. Let \( R_L \) be the last point in our discretization of \( R \) (so that the boundary of the area containing \( R_L \) includes the junction of the ESM with the dendritic shaft). Then a discretization of the boundary condition (11) yields the following equation for \( R_{L+1} \):

\[
-\Omega D_z \frac{R_{L+1} - R_L}{\Delta z} = \frac{R_{L+1} + R_L}{2} - R_0
\]

where this time \( R_0 \) represents the concentration of receptors on the dendritic shaft. The solution of this equation is

\[
R_{L+1} = \frac{(\theta - 1)R_L + 2R_0}{\theta + 1},
\]

where \( \theta = 2\Omega D_z/\Delta z \). The discretized flux is therefore

\[
-D_z \frac{R_{L+1} - R_L}{\Delta z} = \frac{2D_z(R_L - R_0)}{2\Omega D_z + \Delta z}
\]

which is again second-order accurate and independent of the extrapolated value \( R_{L+1} \).
4 AMPA receptor trafficking under basal conditions

4.1 Steady-state AMPA receptor concentrations and fluxes

For fixed parameter values there is a unique steady-state solution, which is obtained by setting the right-hand sides of equations (1-8) to zero. First, equations (3,4) imply that in the steady-state the free and bound receptor concentrations within the PSD are related according to

\[ Q_I = \frac{\rho_I (1 - \rho_{II})}{1 - \rho_I \rho_{II}} L, \quad Q_{II} = \frac{\rho_{II} (1 - \rho_I)}{1 - \rho_I \rho_{II}} L \]  

(21)

where

\[ \rho_j(r) = \frac{P_j(r)}{P_j(r) + \alpha_j/\beta_j} \]  

(22)

for \( j = I, II \). It remains to solve the following steady-state diffusion equations for the free receptor concentrations:

\[ 0 = D_r \frac{\partial}{\partial r} \left( r \frac{\partial P_j}{\partial r} \right) + \sigma_{II} \delta_{j,II}, \quad 0 \leq r < r_0 \]  

(23)

and

\[ 0 = D_z \frac{\partial^2 R_j}{\partial z^2} + \frac{\sigma_I}{A_z} \delta_{j,II} - k_j R_j, \quad 0 < z < z_0 \]  

(24)

for \( j = I, II \), subject to the boundary conditions (9,11). Here \( \delta \) is the Kroncker delta function. One finds that the general steady-state solution for type I receptors is

\[ P_I(r) = c_1 \ln(r) + c_2, \]  

(25)

\[ R_I(z) = c_3 e^{\mu z} + c_4 e^{-\mu z} + \Sigma_I, \]  

(26)

where \( \mu = \sqrt{k_I/D_z} \) and \( \Sigma_I = \sigma_I/(A_z k_I) \). Finiteness of \( P_I \) requires \( c_1 = 0 \), and hence the vanishing of the steady-state flux at the boundary between the PSD and ESM. The boundary condition (9) for \( j = I \) implies \( c_3 = c_4 \) and \( c_2 = 2 c_3 + \Sigma_I \). The boundary condition (11) for \( j = I \) yields the result

\[ c_3 = \frac{R_{I,0} - \Sigma_I}{e^{\mu z_0} + e^{-\mu z_0} + D_z \mu \Omega_I(e^{\mu z_0} - e^{-\mu z_0})}. \]
Similarly, the steady-state solution for type II receptors is given by

\[ P(r) = d_1 \ln(r) + d_2 - \Sigma_{II} r^2 \]  
(27)

\[ R(z) = d_3 e^{\nu z} + d_4 e^{-\nu z} \]  
(28)

where \( \nu = \sqrt{k_{II}/D_z} \) and \( \Sigma_{II} = \sigma_{II}/(4A_r D_r) \). Finiteness of \( P_{II} \) requires \( d_1 = 0 \). The boundary conditions (9,11) for \( j = II \) then show that

\[ d_2 = d_3 + d_4 + \Sigma_{II} r_0^2 + \frac{2D_r \Sigma_{II} r_0}{h_{II}}, \]  
(29)

\[ d_3 = d_4 - \frac{2D_r \Sigma_{II} r_0}{D_z \nu}, \]  
(30)

\[ d_4 = \frac{R_{II,0} + 2e^{\nu z_0}(D_z \nu \Omega_{II} + 1)D_r \Sigma_{II} r_0/(D_z \nu)}{2[\cosh(\nu z_0) + D_z \nu \Omega_{II} \sinh(\nu z_0)]}. \]  
(31)

With both \( P_I \) and \( P_{II} \) known, we can now solve for \( Q_I \) and \( Q_{II} \) using equations (21).

Typical steady-state concentration profiles are shown in Figure 12A for parameter values corresponding to a synapse operating under basal conditions (listed in Table 1). The total receptor concentration in the PSD is high and almost entirely composed of GluR2/3 receptors (number of GluR1/2 receptors in PSD \( \approx 1 \), number of GluR2/3 receptors \( \approx 37 \)), with about half of these bound (number of bound receptors \( \approx 20 \)). The concentration drops dramatically into the ESM and is almost entirely composed of GluR1/2 receptors (number of GluR2/3 receptors in ESM \( \approx 1 \), number of GluR1/2 receptors \( \approx 16 \)). The steady-state is maintained primarily by the constitutive recycling of GluR2/3 receptors, which involves a constant flux of receptors from the PSD to the ESM where they are endocytosed and either reinserted into the membrane surface or degraded. The spatial dependence of the surface receptor flux is also shown in Figure 12A, where a positive (negative) flux represents flow away from (to) the PSD. The receptor flux is positive throughout the membrane, increasing from zero at the center of the PSD, peaking at \( \approx 0.13 \mu m^{-1}s^{-1} \) at the PSD-ESM junction and decreasing to \( \approx 0.003 \mu m^{-1}s^{-1} \) at the ESM-shaft junction. Note that the flux of free receptors is continuous at the boundary between the PSD and ESM. The discontinuous jump in receptor concentration at this boundary is due to two
Figure 12: Steady-state behavior under basal conditions (see Table 1 for parameter choices). (A) Steady-state concentration and flux of surface AMPA receptors. The shaded and unshaded regions are the PSD and ESM, respectively. Distance is measured from the center of the PSD, and is given by the radial coordinate $r$ within the PSD (0 to 0.2 mm) and by $r_0 + z$ within the ESM (0.2 to 1.2 mm), where $z$ is the axial distance from the PSD (see Figure 11). (B-F) Dependence of the steady-state number of AMPA receptors in the PSD on model parameters.
factors: bound receptors within the PSD do not equilibrate with the free receptor concentration in the ESM, and the boundary acts as a barrier to receptor movement. All of these features of the concentration and flux are consistent with experimental data (see Section 2.4).

Given the steady-state receptor concentrations, it is straightforward to calculate the total number of type I and type II AMPA receptors in the PSD and ESM by integrating over the corresponding spatial domain. If we assume that the strength of the synapse is proportional to the total number of synaptic receptors, then we can determine how the steady-state synaptic strength depends on the various parameters of the model. The results are shown in Figures 12B-F. Since we are assuming that the constitutive recycling of GluR2/3 receptors predominates under basal conditions, the total receptor number in the PSD tends to be insensitive to changes in parameters associated with GluR1/2 trafficking except for the rates of exo/endocytosis $\sigma_I$ and $k_I$. On the other hand, the receptor number is strongly dependent on parameters associated with GluR2/3 trafficking, including the rates of exo/endocytosis, $\sigma_{II}$, $k_{II}$, the ratio of the binding and unbinding rates, $\alpha_{II}/\beta_{II}$, and the hopping rate $h_{II}$.

4.2 Blocking exo/endocytosis

We next attempt to reproduce the experiments of Luscher et al. [41] (see Section 2.4). We do this in our model by setting to zero either exocytosis ($\sigma_I, \sigma_{II}$) or endocytosis ($k_I, k_{II}$), and determining the resulting time-dependent decrease or increase in the number of synaptic receptors. We find that blocking exocytosis without changing any other parameters of the model leads to a loss of about half of the receptors in the PSD (see Figure 13A). In order to obtain the correct change in receptor number when blocking endocytosis, however, we also have to raise the background concentration $R_{II,0}$ of type II receptors within the dendritic shaft (we choose $R_{II,0} = 10 \mu m^{-2}$). This is motivated by the idea that blocking endocytosis within the dendrite of a cell raises the background
Figure 13: Time course of AMPA receptors after blocking exo/endocytosis. (A) Blocking endocytosis. With receptors at basal steady-state at time \( t < 0 \), endocytosis is blocked by setting \( k_j = 0 \) (\( j = I, II \)) at \( t = 0 \). The background concentration \( R_{II,0} \) is also set to 10µm\(^{-2}\) at the same time, representing concurrent blockage at nearby synapses. The number of AMPA receptors in the PSD nearly doubles within 30 min (due to an increase in the number of free receptors) and reaches a new steady-state value of approximately 84 receptors in 1 hr (not shown). (B) Blocking exocytosis. This time, exocytosis is blocked by setting \( \sigma_j = 0 \) (\( j = I, II \)) at \( t = 0 \). The number of AMPA receptors in the PSD almost halves in less than 10 min (due to a loss of free receptors). These results are consistent with Luscher et al. [41] (see Figure 10).
concentration of AMPA receptors across multiple synapses. We then find a doubling of receptors in the PSD after endocytosis is blocked (see Figure 13B). Interestingly, if we assume that the number of synaptic AMPA receptors is proportional to the amplitude of elicited EPSPs, then the time courses predicted by our model are also similar to those found by Luscher et al. (see Figure 10), although the reduction in response to exocytic blockage is slightly faster in our model and the increase in response to endocytic blockage is slightly slower. Note that the particular mechanism implemented by our model involves the removal or addition of free receptors within the PSD. For physiologically reasonable diffusivities and basal rates of exo/endocytosis, the boundary conditions play a crucial role in generating a sufficiently large free receptor concentration within the PSD that is sensitive to the rates of exo/endocytosis. Our model also predicts that when exocytosis is completely blocked the number of synaptic receptors should continue to decrease at a slow rate over several hours. This slower component represents the unbinding of receptors from scaffolding proteins and their ultimate escape from the PSD to the ESM boundary.
5 AMPA receptor trafficking during LTP/LTD

5.1 Trafficking during LTP

Motivated by the experimental findings described in Section 2.4, we numerically solve the differential equations of our receptor trafficking model in order to determine the time-dependent variation in the GluR1/2 receptor concentration in response to changes in the rate of exocytosis and the concentration/affinity of active binding sites in the PSD. We assume that such changes occur rapidly relative to the time course associated with the redistribution of AMPA receptors. This is based upon experimental data indicating that CaMKII, one of the crucial components of the signaling pathways involved in the induction of LTP, acts like a rapid molecular switch [51, 52, 53]). It is important to emphasize, however, that the detailed molecular mechanisms underlying the trafficking of AMPA receptors during LTP are still far from clear. One of the useful features of our mathematical model is that, given a hypothesis regarding the regulation of receptor trafficking during LTP, it allows us to explore the particular role of lateral membrane diffusion in the spatiotemporal redistribution of receptors.

In order to model changes in the rate of exocytosis we set $\sigma_I = \kappa_I S_I$, where $S_I$ is the total number of GluR1/2 receptors in the intracellular pool and $\kappa_I$ is the rate of exocytosis per receptor. We assume that in steady-state the rate of exocytosis is equal to the rate of receptor synthesis, which we denote by $\delta_I$. A sudden increase in $\kappa_I$, and hence $\sigma_I$, results in the rapid insertion of intracellular receptors into the ESM, and a corresponding reduction in $S_I$ so that, after an initial transient, the rate of exocytosis returns to the steady-state value $\delta_I$. (Increasing the rate of receptor synthesis $\delta_I$ would lead to a persistent change in the rate of receptor insertion, but does not produce realistic time courses for LTP). Therefore, in order to maintain an increase in the number of synaptic receptors, we further assume that LTP involves an increase in the concentration $L$ of active binding sites. One proposal for how this could occur is that AMPA receptors delivered to the synapse bring
with them so called “slot” proteins that provide the additional binding sites [16]. Here we consider a simpler model, in which additional binding sites are activated during the induction phase of LTP [17]. Finally, we assume that the interaction between PSD-95 and stargazin facilitates the entry of receptors into the PSD (an enhancement of the hopping rate $h_I$) and increases the binding affinity $\alpha_I$.

In Figure 14 we show snapshots of the GluR1/2 receptor concentration profile and the associated flux in response to a sudden increase in the parameters $\kappa_I$, $L$, $h_I$ and $\alpha_I$ at time $t = 0$. The synapse is assumed to be in steady-state under basal conditions for $t < 0$. Figures 14A-D show a sequence of events in which GluR1/2 receptors are rapidly inserted into the ESM due to a transient increase in the rate of exocytosis, after which they laterally diffuse into the PSD. This leads to a large transient increase in the free synaptic receptor concentration. The free receptors then bind to the newly-activated binding sites within the PSD, leading to a persistent increase in the concentration of bound receptors in the PSD. The trafficking of GluR1/2 receptors into the PSD accounts almost fully for the doubling of the total number of synaptic receptors in the PSD. In Figures 15A-B we plot the corresponding time courses for the total number of receptors in the PSD and ESM. Also shown in Figure 15B is the depletion of the intracellular pool. The number of receptors in the PSD rises to a peak of $\approx 95$ receptors in $\approx 50$ sec, then settles down to $\approx 80$ receptors in another $\approx 250$ sec. This is due mainly to the trafficking of GluR1/2 receptors, although some newly activated binding sites are filled by free GluR2/3 receptors. The number of receptors in the ESM rises transiently due to the exocytosis of intracellular GluR1/2 receptors. Though many ESM receptors enter the PSD, many also diffuse away from the PSD through the junction between the spine and dendritic shaft. If we again assume that the number of synaptic AMPA receptors is proportional to the elicited EPSP amplitudes, then the time course shown in Figure 15A is consistent with recordings from single synapses [26, 27] and populations of synapses [4, 25]. That is, typical EPSPs recorded during LTP show a sharp, initial rise that peaks in $\approx 30-60$ sec at $\approx 200-300\%$
Figure 14: Snapshots of GluR1/2 AMPA receptor concentration and flux during LTP at (A) 10 sec, (B) 30 sec, (C) 60 sec, and (D) 120 sec after induction. Distance is defined as in Figure 12A. With receptors at basal steady-state at time \( t < 0 \), LTP is induced by setting \( L = 477\mu m^{-2} \), \( \alpha_I = 0.001\mu m^2s^{-1} \), \( \kappa_I = 0.0556s^{-1} \), and \( h_I = 0.01\mu m s^{-1} \) at time \( t = 0 \). The concentration in the ESM rises transiently as GluR1/2 receptors from the intracellular pool are exocytosed there. Mediated by diffusion and barrier hopping, the concentration in the PSD rises as receptors from the ESM enter the PSD, and a portion of these receptors are immobilized by the newly-activated binding sites.
Figure 15: Time course of AMPA receptors during LTP. (A,B) Time course of synaptic and extrasynaptic receptors after induction of LTP using same conditions as Figure 14. These results are consistent with experimentally recorded EPSPs after LTP induction, see e.g. [25, 27]. (C,D) Time course of synaptic and extrasynaptic receptors without synaptic targeting. With receptors at basal steady-state at time $t < 0$, the rate of GluR1/2 exocytosis is increased by setting $\kappa_I = 0.0556 \text{ s}^{-1}$ at time $t = 0$. However, the hopping rate and binding affinity of GluR1/2 receptors, and the number of active binding sites remain at basal levels. These results are consistent with Schnell et al. [49]. (E) Exchange of GluR1/2 and GluR2/3 AMPA receptors. After 1 hr of maintaining LTP parameters, all parameters are returned to their basal values except the active binding site concentration $L$, at which time GluR2/3 receptors begin to replace GluR1/2 receptors at active binding sites. These results are consistent with [84].
of the baseline response, then settles at a slower rate to $\approx 150\text{-}200\%$ of baseline response. In Figures 15C,D we show the time-dependent variation in the number of synaptic and extrasynaptic receptors in response to changes in the rate of exocytosis alone, without a corresponding increase in active binding sites, binding affinity or hopping rate. The concentration in the ESM rises transiently as GluR1/2 receptors from the intracellular pool are exocytosed there, as in the case of LTP, but now there is only a small transient rise in the number of synaptic receptors. These results illustrate that both exocytosis and synaptic targeting are required for LTP, and are consistent with what happens when there is an overexpression of stargazin without a corresponding increase in PSD-95 [49]. That is, stargazin can facilitate transport of AMPA receptors to the surface but is not able to target synapses unless it can interact with PSD-95.

It is important to emphasize that the distribution of receptors has not reached a steady-state over the time course of a few minutes shown in Figures 14 and 15A,B. For during this period the rate of exocytosis has returned to its basal levels, which implies that there are not enough free GluR1/2 receptors to maintain equilibrium with the receptors bound to the newly activated binding sites within the PSD. Thus over a longer time period of several hours, the GluR1/2 receptors are slowly exchanged with GluR2/3 receptors through the process of constitutive recycling (see Figure 15E). Such an exchange has been observed experimentally, and has been suggested as a mechanism for maintaining bidirectional synaptic plasticity [84].

### 5.2 Trafficking during LTD

We numerically solve the extended receptor trafficking model (see Section 3.2) to determine the time-dependent variation in synaptic receptor concentration during LTD. We assume that a low frequency stimulus is applied for 900 sec and during that period a fraction of GRIP-associated GluR2/3 receptors are converted to PICK-associated receptors. Since the latter are assumed to have a higher unbinding rate, they tend to be
removed from the PSD. Figures 16A-D show snapshots of the resulting GluR2/3-GRIP and GluR2/3-PICK receptor concentration profiles within the PSD, and the associated fluxes. The synapse is assumed to be in steady-state under basal conditions for $t < 0$, with

![Figure 16: Snapshots of GluR2/3-GRIP and GluR2/3-PICK AMPA receptor concentrations and fluxes during LTD at (A) 0 sec, (B) 60 sec, (C) 900 sec, and (D) 1200 sec after onset of a low frequency stimulus that lasts 900 sec. Distance is defined as in Figure 12A. With receptors at basal steady-state at time $t < 0$, LTD is induced by simulating the extended LTD model for 900 sec, beginning at time $t = 0$. LTD parameter values are $\mu = 10^{-4}$ s$^{-1}$, $\nu = 0.01$ s$^{-1}$, $\beta_{II}^* = 0.1$ s$^{-1}$, $k_{II}^* = k_{II} = 0.1667$ s$^{-1}$, and $\gamma = 0.001$ s$^{-1}$. After 900 sec, $\mu$ is set to zero so that the remaining PICK is converted back to GRIP. The concentration of GluR2/3-GRIP decreases while GluR2/3-PICK increases during the early course of LTD, and then both decrease together until 900 sec, when GluR2/3-PICK begins to convert back to GluR2/3-GRIP. However, the final concentration of GluR2/3-GRIP is lower than the initial concentration, due to a loss of active binding sites.

a negligible concentration of PICK-associated receptors. It can be seen that there is a conversion of GRIP to PICK during the presentation of the stimulus, with a partial recovery after the stimulus is removed. The steady-state receptor concentration has decreased,
however, due to the removal of active binding sites. This is further illustrated in Figure 17A, where the time course of the total number of receptors is plotted for the various receptor types. Interestingly, our model can reproduce a variety of experimental results. For example Dudek and Bear [24] showed that increasing the frequency of the stimulus from 3Hz to 10Hz, say, can lead to a transient reduction in synaptic strength rather than LTD. One way to generate this in our model is to assume that the stimulus induces the conversion of GRIP to PICK but the number of active binding sites is not reduced (see Figure 17B). In another experiment, Dudek and Bear [85] showed how a sequence of low frequency stimulations each separated by \( \approx 45 \text{ min} \) can induce a saturating sequence of LTD. This result can also be reproduced by our model, with the saturation arising from the fact that even if most binding sites are removed, there are still free receptors present.
Figure 17: Time course of AMPA receptors during LTD. (A) Time course of receptors in the PSD during LTD with low frequency stimulus. LTD is induced as in Figure 16. Bound GluR2/3-GRIP is rapidly converted to bound GluR2/3-PICK and released during the first few minutes of LTD. Notice how the number of active binding sites follows the loss of bound receptors. LTD induction ends at 900 sec and GluR2/3-PICK rapidly converts back to GluR2/3-GRIP. However, the new steady-state number of receptors in the PSD is much lower due to the loss of active binding sites. The variation in the number of synaptic receptors is consistent with typical EPSP recordings during LTD, e.g. Dudek and Bear [24]. (B) Time course of receptors in the PSD during LTD with moderate frequency stimulus. LTD is induced as in Figure 16, except $\gamma = 0$. Though similar to A, the number of active binding sites remains unchanged, so that the number of AMPA receptors in the PSD returns to its initial value after LTD induction terminates. This is consistent with Dudek and Bear [24]. (C) Saturation of LTD. LTD is induced as in Figure 16, except that it is followed by 45 min of basal activity, and this one hour epoch is repeated three times, followed by the induction of LTP. Notice that the total loss of receptors in the PSD decreases in each consecutive epoch, since the loss is proportional to the number of active binding sites at the beginning of each epoch. This is consistent with Dudek and Bear [85].
6 Discussion

In this paper we have presented a mathematical model of AMPA receptor trafficking at the synapse. The model provides a general theoretical framework for investigating the nature of AMPA receptor trafficking under basal conditions and its role in the expression of synaptic plasticity. The behavior of the model depends on various trafficking parameters that could be targets of the second-messenger pathways activated by the postsynaptic calcium signal during the induction of LTP or LTD. We have used our model to explore the consequences of targeting different sets of trafficking parameters, and have shown how this can reproduce a wide range of experimental data: (1) The increase/decrease in synaptic strength after pharmacologically blocking exo/endocytosis [41]. (2) The time course of changes in synaptic strength during the expression of LTP [2, 25, 27]. (3) The slow exchange of GluR1/2 receptors with GluR2/3 receptors after potentiation [84]. (4) The time course of changes in synaptic strength during the expression of LTD and its dependence on frequency of stimulation [24, 85]. (5) The saturation of LTD induced by a sequence of low frequency stimuli [85].

Constraining our model to reproduce all of these results using physiologically reasonable values for the various parameters allows us to make experimentally testable predictions regarding AMPA receptor trafficking and its regulation during LTP/LTD. First, there should be a significant fraction of mobile receptors in the PSD under basal conditions, which is consistent with the data of Groc et al. [38] and Ashby et al. [40]. This, in turn, requires a barrier to diffusion at the PSD-ESM boundary, as previously suggested by Triller and Choquet [17, 23]. Second, the exocytosis of intracellular GluR1/2 receptors during LTP only generates realistic time courses if it is combined with synaptic targeting (e.g., increases in the hopping rate across the PSD-ESM barrier and the rate of binding to scaffolding proteins). This is consistent with the suggested role of stargazin and its interaction with PSD-95 [49]. Moreover, depletion of the intracellular pool suggests that the increased rate of receptor insertion is only temporary. Therefore, in order to have
persistent early-phase LTP, it is necessary to increase the number of active binding sites within the PSD, perhaps via the delivery of “slot” proteins by incoming AMPA receptors [55, 16]. Third, the unbinding of GluR2/3 receptors from scaffolding proteins in the PSD (perhaps by exchange of GRIP with PICK) and subsequent endocytosis from the ESM is not sufficient to generate persistent LTD. A realistic time course for LTD can be generated, however, if there is also a gradual decrease in the number of active binding sites, that is, a removal of “slot” proteins. One of the interesting features of our model is that a number of experimental results can be obtained without any further tuning of the model. These include the slow exchange of GluR1/2 with GluR2/3 receptors during LTP (Figure 15E) and the saturation of LTD (Figure 17C).

6.1 Model simplifications

We recognize that in constructing our model we have made a number of simplifications, and some of our results and conclusions may be a consequence of them. We now wish to explore the implications of these simplifications in detail.

Dendritic spine geometry and junctions. One simplification is our choice of a uniform cylinder as a model for the postsynaptic membrane of the dendritic spine, as well as the boundary conditions representing the junctions of the PSD with the ESM and the spine with the dendritic shaft. Although the spine head near the PSD is roughly cylindrical [34], the junction of the PSD with the ESM does not generally occur at the boundary of the cylinder body and end disk; instead, this junction typically resides in the interior of the end disk, and the ESM experiences a small radius of curvature through the transition of the end disk to the cylinder body. It is known that such curvatures can impede receptor movement in the membrane [75]. Given the simplified geometry, we found it necessary to treat the PSD-ESM junction as a barrier to receptor movement in order to maintain a free receptor concentration in the PSD consistent with experimental data. We represented the
barrier by constraining the net flux across the junction to be proportional to the difference in concentrations on either side of it, and called the proportionality constant the hopping rate. Thus the hopping rate limits the flux across the PSD-ESM junction and allows the free receptor concentrations to be discontinuous there. In assuming such a barrier, we are keeping with the views of Triller and Choquet [17, 23] who suggest that synaptic localization of receptors results not only from interactions with scaffolding proteins, but from other factors such as interactions with submembrane cytoskeletal corrals and transmembrane protein pickets, and transient associations with other receptors and membrane lipids. It should be noted, however, that we have introduced the effects of these factors only at the PSD-ESM junction as a homogenous hopping rate, while Triller and Choquet imply that these factors are present throughout the entire PSD. These interior factors could be included in our model by modifying the effective diffusivities in the PSD [76].

We have also taken the net flux across the junction of the spine with the dendritic shaft to be proportional to a difference in receptor concentrations. Here, however, we have simplified our model by “collapsing” the compartment associated with the spine neck. Thus the flux is proportional to the difference in the receptor concentration at the border of the spine head and the background concentration found in the membrane of the dendritic shaft. The proportionality constant is now interpreted as an inverse diffusive impedance, which arises from the surface effects of the spine neck and junction, including curvature and narrowing. We have further simplified our model by ignoring the dynamics of receptor trafficking in the dendritic shaft, taking the concentration in the shaft to be constant. This assumption will have to be relaxed when considering trafficking across multiple synapses (see below under heading “Multiple synapses and homeostatic plasticity”).

Scaffolding and receptor-scaffold clusters. Much is still unknown about the nature of the association of AMPA receptors with scaffolding proteins. Although a number of
scaffolding-related proteins and their various interaction domains have been identified [15], little is known about how these proteins act in concert to regulate and maintain AMPA receptor numbers at synapses and elsewhere. In our model we have approached this issue phenomenologically by employing active binding sites. These represent protein complexes able to immobilize AMPA receptors, and are much like the “slot” proteins hypothesized by Shi et al. [55] (see also [16]), although we also include the possibility that these binding sites can exist in an activated or deactivated state. We have further simplified this issue by assuming that active binding sites exist in uniform concentrations only at the PSD and do not explicitly model the trafficking/activation of these sites. Choquet and Triller [17, 18], however, argue that scaffolding proteins exist outside the PSD and that receptors can bind to these proteins extrasynaptically, creating large receptor-scaffold clusters that then diffuse together as a single entity. The diffusivity of such clusters is smaller than that of a single receptor, not directly because of the increased physical size of a cluster compared to a single receptor [86], but indirectly through the increased interactions with corrals and pickets.

**Signaling cascades.** It is well known that the induction phase of LTP/LTD produces a transient postsynaptic calcium signal that triggers second-messenger signaling cascades responsible for the expression of LTP/LTD [7]. For simplicity, we have not included these signaling dynamics in our model, since we have focused on AMPA receptor trafficking during the expression of LTP/LTD. Evidence suggests that the induction of LTP happens in a fast, switch-like manner (on the order of a few seconds), and is dependent on the bistability of the calcium-activated enzyme CaMKII [51, 52, 53]. Thus the time scale of the induction phase of LTP is much shorter than that of the expression phase of LTP, which occurs on the order of minutes. This separation of time scales allows us to treat the targeted LTP parameters as switches. One may argue that treating the increase in the number of active binding sites during LTP as a switch is invalid, since active binding sites may need to be transported to the PSD from other regions of the postsynaptic cell.
However, similar receptor time courses will be observed if active binding sites are trafficked to the PSD at approximately the same rate as the newly-exocytosed GluR1/2 heteromers enter the PSD (e.g., if these receptors bring new binding sites with them). Similarly, the induction of LTD requires the activation of enzymes like PKC, calcineurin and PP1 [88, 15, 89]. We also treated the activation of these signaling cascades as switches, although unlike CaMKII, their activity persists only for the duration of the low frequency stimulus that maintains the Ca^{2+} signal, and promptly inactivate with the termination of this signal.

6.2 Future directions

Our model can be extended and modified in a number of ways, potentially offering insights into a larger collection of AMPA receptor trafficking data.

Multiple synapses and homeostatic plasticity. Conceptually, it is rather straightforward to extend our current single synapse model to a model of multiple synapses on a common dendritic shaft. This would allow for the exploration of, among other data, the recent results of Adesnik et al. [39], who report a much slower rate of constitutive recycling at the synapse, and that the rapid exchange of surface AMPA receptors with intracellular pools does not occur at the dendrite, but at the cell body, where exocytosed receptors rapidly diffuse along the dendritic membrane towards synapses. Such a model, however, would be challenging to analyze or even to simulate. We have developed a mesoscopic version of the model presented in this paper that maintains our single synapse dynamics while allowing us to more easily incorporate additional synapses and membrane. Besides studying the data of Adesnik et al., we can use the multi-synapse model to explore the role of AMPA receptor trafficking in homeostatic plasticity [90, 91, 92, 93, 94, 95]. One of the major mechanisms of global homeostatic plasticity is known as synaptic scaling, in which all synapses gain (lose) strength multiplicatively, proportional to the level of
decrease (increase) in average network activity. Although a number of pre- and postsynaptic mechanisms have been implicated in synaptic scaling, experimental data points to the regulation of synaptic AMPA receptor numbers as a critical component in CNS synaptic scaling. O’Brien et al. [90] find that the number of synaptic AMPA receptors increases (decreases) with decreased (increased) activity levels, and that decreasing activity reduces that turnover rate of GluR1 subunits. Ehlers [92] has shown that changes in cortical activity leading to synaptic scaling also cause a remodeling of the PSD that could yield changes in the number of synaptically-expressed AMPA receptors which are consistent with the direction and magnitude of the scaling. These results suggest that synaptic scaling could be due to mechanisms similar to those used in the expression of LTP/LTD, such as regulation of the balance of exo/endocytosis, the number of active binding sites, or the hopping rate. However, unlike the rapid changes in AMPA receptor numbers that accompany LTP/LTD, synaptic scaling occurs slowly, requiring hours and even days to be expressed [90, 91]. Nevertheless, the possible AMPA receptor trafficking targets of synaptic scaling can be explored within our mesoscopic model; indeed, our analysis suggests that the up- or down-regulation of exocytosis can produce a multiplicative scaling of the number of AMPA receptors at each synapse. Interestingly, the trafficking of NMDA receptors has also been implicated in such homeostatic plasticities as synaptic scaling and metaplasticity (see [96] for a review). Without much adjustment, our model can be used to study the trafficking of NMDA receptors as well, highlighting again the utility of our theoretical receptor trafficking framework.

Spatially-uniform concentration approximation. Given that the typical length-scale of a dendritic spine is $l_{sp} = 0.1 \mu m$, it follows that the typical time-scale $\sqrt{l_{sp}^2/D}$ of diffusion within the PSD and ESM is 10 and 1 sec, respectively. Hence the flux of AMPA receptors due to lateral diffusion is fast compared to the time-scale (minutes) of the hopping and exo/endocytic fluxes, even during the expression of LTP/LTD. We can therefore treat the various receptor concentrations within the PSD and ESM as being
spatially uniform, reducing our model system of partial differential equations (PDEs) to a system of ordinary differential equations (ODEs). This has two major advantages. First, systems of ODEs are typically easier to analyze and numerically simulate than PDEs, providing us an even broader range of inquiry. Second, a master equation governing the probabilities of individual receptor trafficking events can be derived from the system of ODEs. This will allow us to explore, for example, the consequences of stochastic fluctuations in the receptor fluxes constituting constitutive recycling, or calculate the variance in receptor numbers as the system approaches a new steady-state during the expression of LTP/LTD. Such modeling could, for instance, help explain the noise associated with EPSP recordings.

**Discrete synaptic states.** Recent work suggests that synaptic plasticity at excitatory synapses in the CNS occurs as a transition between discrete, electrophysiologically-defined states [97, 27], and that the transition is expressed through AMPA receptor trafficking. Montgomery and Madison [98] define five such states: active, potentiated, depressed, silent, and recently silent. The **active** state displays both AMPA and NMDA receptor responses and can undergo only NMDA receptor-mediated LTP or LTD. The active state can transition into the potentiated, depressed or silent state. The **potentiated** state can be depotentiated (i.e.; return to the active state) only through metabotropic glutamate receptor-mediated depression. The **depressed** state is currently ill-defined and may differ little from the active state. The **silent** state manifests NMDA receptor responses, but not AMPA receptor responses due to the lack of membrane-expressed postsynaptic AMPA receptors. Silent synapses cannot be depressed (they are in a sense already depressed), but can be potentiated, leading to the **recently silent** state. The recently silent state shows both AMPA and NMDA receptor responses like the active state, but, unlike the active state, it cannot be depressed. The recently silent state spontaneously transitions into the active state \(\approx 30\) minutes after being unsilenced. Montgomery and Madison argue that the discrete synaptic state model improves upon the continuum model of synaptic strength.
by increasing the information-carrying capacity of a synapse, since a synapse retains a history of recent state transitions, and by providing a wider range of dynamic responses to pre- and postsynaptic activity. In terms of discrete states, we have studied in this paper the active state of a single synapse, and its transitions into the potentiated or depressed state. One can also study the other four synaptic states and their possible transitions within our model (or within the ODE model described in the preceding paragraph) by assigning parameter behaviors in each case. For instance, the silent synaptic state could be realized by decreasing the type II exocytic rate and removing active binding sites, while the transition from the silent into the recently silent state can be simulated in a manner similar to our LTP simulations. Using similar techniques, our model can also be used to simulate the results of O’Connor et al. [27] in which the potentiation/depotentiation of a large population of synapses can be decomposed into discrete, step-like transitions of single synapses. As these transitions appear to occur stochastically, our ODE model described above is particularly suited to modeling O’Connor et al.’s data.
References


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