

1 Competition for synaptic building 2 blocks shapes synaptic plasticity

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7
8 **Abstract** Changes in the efficacies of synapses are thought to be the neurobiological basis of
9 learning and memory. The efficacy of a synapse depends on its current number of
10 neurotransmitter receptors. Recent experiments have shown that these receptors are highly
11 dynamic, moving back and forth between synapses on time scales of seconds and minutes. This
12 suggests spontaneous fluctuations in synaptic efficacies and a competition of nearby synapses for
13 available receptors. Here we propose a mathematical model of this competition of synapses for
14 neurotransmitter receptors from a local dendritic pool. Using minimal assumptions, the model
15 produces a fast multiplicative scaling behavior of synapses. Furthermore, the model explains a
16 transient form of heterosynaptic plasticity and predicts that its amount is inversely related to the
17 size of the local receptor pool. Overall, our model reveals logistical tradeoffs during the induction of
18 synaptic plasticity due to the rapid exchange of neurotransmitter receptors between synapses.

20 Introduction

21 Simple mathematical models of Hebbian learning exhibit an unconstrained growth of synaptic
22 efficacies. To avoid runaway dynamics, some mechanism for limiting weight growth needs to be
23 present. There is a long tradition of addressing this problem in neural network models using synaptic
24 normalization rules (*Malsburg, 1973; Oja, 1982; Miller and MacKay, 1994; Wu and Yamaguchi, 2006;*

25 *Lazar et al., 2009*). Obviously, in order to keep up with the pace of synaptic changes due to
26 Hebbian plasticity, normalization mechanisms must act sufficiently fast. Slow homeostatic synaptic
27 scaling mechanisms (*Turrigiano et al., 1998*) may therefore be ill-suited for ensuring stability (*Wu*
28 *and Yamaguchi, 2006; Zenke et al., 2013; Chistiakova et al., 2015*). A particularly interesting fast
29 normalization rule scales synapses multiplicatively such that the sum of synaptic weights remains
30 constant. Attractive features of such a rule, next to its conceptual simplicity, are that the relative
31 strength of synapses are maintained and that in combination with Hebbian mechanisms it naturally
32 gives rise to lognormal-like weight distributions as observed experimentally (*Song et al., 2005;*
33 *Loewenstein et al., 2011; Zheng et al., 2013; Miner and Triesch, 2016*). While such normalization
34 mechanisms are not considered biologically implausible, their link to neurobiological experiments
35 has been tenuous.

36 In a recent review, *Chistiakova et al. (2015)* argue that so-called heterosynaptic plasticity (*Lynch*
37 *et al., 1977; Bailey et al., 2000; Jedlicka et al., 2015; Antunes and Simoes-de Souza, 2018*) may be a
38 prime candidate for such a fast synaptic normalization scheme. The term “heterosynaptic” plasticity
39 is used in contrast to the much more widely studied “homosynaptic” plasticity, where changes
40 occur in a stimulated synaptic pathway. In contrast, heterosynaptic plasticity refers to changes in
41 synaptic efficacies that occur in an unstimulated pathway after the stimulation of a neighboring
42 pathway. The most common form of heterosynaptic plasticity has a homeostatic nature: if synapses
43 in stimulated pathways potentiate, then this is accompanied by a depression of unstimulated
44 pathways. Conversely, if synapses in stimulated pathways depress, this is accompanied by a
45 potentiation of unstimulated pathways. A classic example of this has been observed in intercalated
46 neurons of the amygdala (*Royer and Paré, 2003*).

47 Interestingly, such homeostatic regulation is also consistent with findings at the ultra-structural
48 level. The physical size of a synapse, in particular the surface area of the postsynaptic density (PSD),
49 is commonly used as a proxy for a synapse's efficacy (*Chen et al., 2015; Bartol et al., 2015*). *Bourne*
50 *and Harris (2011)* have observed coordinated changes in PSD surface areas of dendritic spines
51 in the hippocampus after LTP induction. They report that increases in the PSD surface areas of
52 some synapses or the creation of new synapses are balanced by decreases of PSD surface areas of
53 other synapses or their complete elimination such that the total amount of PSD surface area stays
54 approximately constant. Recent findings support the idea that such regulation may occur at the
55 level of individual dendritic branches (*Barnes et al., 2017*).

56 A proxy of synaptic efficacy that is more precise than PSD surface area is the number of AMPA
57 receptors (AMPARs) inside the PSD. AMPARs are glutamate-gated ion channels responsible for most
58 fast excitatory transmission in the vertebrate brain. During various forms of plasticity the number
59 of these receptors at synapses is modified, leading to changes in synaptic efficacies, reviewed by
60 *Chater and Goda (2014)*. Therefore, a full understanding of synaptic plasticity requires a careful
61 description of the mechanisms that regulate AMPAR numbers in synapses.

62 Here we show how the behavior of keeping the sum of synaptic efficacies approximately constant
63 on short time scales naturally arises from a generic model in which individual synapses compete
64 for a limited supply of synaptic building blocks such as AMPARs or other protein complexes that
65 are necessary to stabilize AMPARs inside the PSD. We assume that there is a local dendritic store
66 of these building blocks and that they enter and leave dendritic spines in a stochastic fashion.
67 The model predicts that the redistribution of synaptic efficacies should act multiplicatively, as is
68 often assumed in *ad hoc* normalization models. We also show that this model naturally gives rise
69 to a homeostatic form of heterosynaptic plasticity, where synapses grow at the expense of other
70 synapses. To this end, we introduce a model of homosynaptic LTP describing the time course
71 of the incorporation of new receptors and slots during LTP induction. Finally, we quantify the
72 scale of spontaneous synaptic efficacy fluctuations due to the fast stochastic exchange of AMPARs
73 between the dendritic pool and postsynaptic receptor slots. We show that small synapses exhibit
74 relatively stronger efficacy fluctuations, which are further accentuated if the local receptor pool is
75 small. Overall, the model reveals how the dynamic behavior of neurotransmitter receptors plays an
76 important role in shaping synaptic plasticity.

77 Results

78 Formulation of the model

79 The architecture of the model is shown in Fig. 1. We consider a piece of dendrite with $N \in \mathbb{N}$
80 synaptic inputs. Each synapse is characterized by two variables. First, each synapse $i \in 1, \dots, N$ has
81 a number of slots $s_i \in \mathbb{R}^{\geq 0}$ for neurotransmitter receptors. Second, at any time a certain number of
82 slots $w_i \in \mathbb{R}^{\geq 0}$ actually contain a receptor. w_i determines the current weight or efficacy of a synapse.
83 We assume that the PSD cannot hold more functional receptors than there are slots, i.e., $w_i \leq s_i$. At
84 the synapses AMPARs are clustered inside PSDs into nanodomains of about 70 nm that contain on
85 average 20 receptors (*Nair et al., 2013*). Interestingly, those postsynaptic nanodomains are aligned

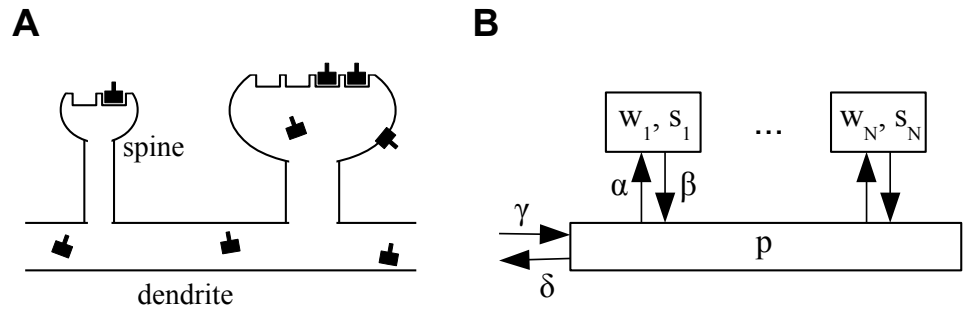


Figure 1. A. Sketch of the architecture of the model. Neurotransmitter receptors, e.g. AMPA receptors, are trafficked through the dendrite and bind to “slots” inside of dendritic spines. The efficacy of a synapse is assumed to be proportional to the number of receptors attached to its slots. **B.** Abstract description of the stochastic process indicating the rates at which receptors move in and out of slots in the synapses and the receptor pool in the dendrite. See text for details.

86 with presynaptic release sites forming so-called nanocolumns. It is noteworthy that AMPARs have
 87 low affinity for glutamate such that receptors outside of nanodomains are unlikely to participate
 88 in synaptic transmission (*Liu et al., 1999; Biederer et al., 2017*). Next to receptors in the synapses,
 89 the neuron maintains a pool of receptors freely diffusing at the neuron surface and ready to be
 90 stabilized inside nanodomains. The size of this pool is denoted $p \in \mathbb{R}^{\geq 0}$. Note that for mathematical
 91 convenience we here consider the s_i , w_i and p to be real numbers that can take non-integer values.
 92 In the stochastic version of the model introduced below these will be natural numbers.

93 Receptors can transition from the pool to empty slots in a synapse or detach from such a slot
 94 and return into the pool with rates $\alpha \in \mathbb{R}^{> 0}$ and $\beta \in \mathbb{R}^{> 0}$, respectively. Receptors in the pool are
 95 removed with a rate $\delta \in \mathbb{R}^{> 0}$ corresponding to internalization of the receptors from the cell surface
 96 (endocytosis). To counteract this loss, new receptors are added at a rate $\gamma \in \mathbb{R}^{> 0}$ and injected into
 97 the pool corresponding to externalization of the receptors to the cell surface (exocytosis). In the
 98 limit of large receptor numbers, the dynamics of the system can be described by the following
 99 system of coupled ordinary nonlinear differential equations:

$$\dot{w}_i = -\beta w_i + \alpha p(s_i - w_i), \quad i = 1, \dots, N \quad (1)$$

$$\dot{p} = -\delta p + \gamma + \sum_i \beta w_i - \sum_i \alpha p(s_i - w_i). \quad (2)$$

100 In the first equation, $-\beta w_i$ describes the return of receptors from synapse i into the pool. The term
 101 $\alpha p(s_i - w_i)$ describes the binding of receptors from the pool to empty slots in synapse i , which is
 102 assumed to be proportional to both the number of receptors in the pool and the number of free

103 slots in the synapse. In the second equation, $-\delta p$ describes the deletion of receptors from the pool,
104 γ represents the gain of new receptors, $\sum_i \beta w_i$ describes the return of receptors from the synapses
105 into the pool, and finally $-\sum_i \alpha p(s_i - w_i)$ describes the loss of receptors from the pool which bind to
106 free slots in the synapses. Together, this is a system of $N + 1$ coupled ordinary nonlinear differential
107 equations. It is nonlinear, because the equations contain product terms of the state variables, in
108 particular the $p w_i$ terms.

109 The model can be interpreted in different ways. Its generic interpretation is that the “receptors”
110 of the model are AMPA receptor (AMPA) complexes composed of AMPARs and transmembrane
111 AMPAR regulatory proteins (TARPs) such as stargazin. The “slots” are postsynaptic density structures
112 comprising membrane-associated guanylate kinase (MAGUK) proteins such as PSD-95 attached to
113 the postsynaptic membrane, which stabilize AMPARs in the postsynaptic density (PSD) (*Hafner et al.,*
114 *2015; Schnell et al., 2002; Sumioka et al., 2010*). Inside the synapses PSD-95 proteins are highly
115 packed (roughly 300 molecules per PSD) (*Kim and Sheng, 2004*) and largely immobile (*Sturgill et al.,*
116 *2009*). When a receptor enters a synapse binding to one or more immobile PSD-95 proteins results
117 in receptor immobilization. In this generic interpretation of the model, the pool of receptors is the
118 set of AMPARs that diffuse in the plasma membrane and that are captured by the slots. Addition of
119 receptors to the pool then subsumes (some or all of) the processes that assemble AMPARs and
120 prepare them for the insertion into slots: assembly of the receptors from the component subunits,
121 trafficking, attachment of TARPs, externalization, and potentially phosphorylation. Removal from the
122 pool similarly subsumes the set of reverse processes. Several variations of this generic interpretation
123 are possible depending on what exactly we would like to associate with the “receptors” in the model:
124 AMPARs, AMPAR+TARP complexes, AMPAR+TARP complexes that have already been exocytosed,
125 phosphorylated, etc. Essentially, our model is a two step model (production and insertion), but we
126 leave it open for interpretation, what steps in the full chain of events are considered the “production”
127 (subsumed in rate γ) and which steps are considered the “insertion” (subsumed in rate α).

128 Evidently, receptor slots themselves must also be stabilized inside the PSD somehow. A second,
129 maybe somewhat counter-intuitive, interpretation of the model is therefore that it describes the
130 binding and unbinding of receptor slots to what one might consider a *slot for a receptor slot* or
131 simply *slot-for-a-slot*. In this interpretation of the model, the “receptors” in the description above
132 are actually the PSD-95 slot proteins and the “slots” are slots-for-a-slot to which the PSD-95 proteins
133 can attach. The model then describes the trafficking of PSD-95 into and out of the PSD, assuming

134 that available AMPAR complexes are quickly redistributed among PSD-95 slots (compared to the
135 time scale of addition and removal of these PSD-95 slots to the PSD). This interpretation may
136 be particularly useful if the supply of PSD-95 is the limiting factor in determining the number of
137 functional AMPARs bound inside the PSD (*Schnell et al., 2002*). We leave open the question what
138 exactly the slots-for-a-slot might be. It is clear however, that PSD-95 molecules can form stable
139 lattices inside the PSD such that PSD-95 proteins could act as slots for other PSD-95 proteins.

140 Interestingly, the analysis of the model presented in the following does not depend on which
141 interpretation is chosen. The only additional assumption we will make is a separation of time scales
142 between the fast trafficking of the “receptors” into and out of the “slots” and the slow addition and
143 removal of receptors to the pool. Our main results only depend on this qualitative feature of the
144 model. For the first generic interpretation of the model the assumption of a separation of time
145 scales appears justified. If we interpret the receptor pool of the model to comprise AMPARs that
146 have been exocytosed and diffuse in the cell membrane, then the half-life of an AMPAR in the pool is
147 of the order of 10 minutes suggesting $\delta^{-1} = 10 \text{ min} / \ln 2 \approx 14 \text{ min}$ (*Henley and Wilkinson, 2013, 2016*).
148 In contrast, the time an AMPAR stays inside the PSD, which we interpret as the time the AMPAR is
149 bound to a slot, appears to be of the order of maybe 30 seconds (*Ehlers et al., 2007*), suggesting
150 $\beta^{-1} = 30 \text{ s} / \ln 2 \approx 43 \text{ s}$. We summarize these and other parameters of the model in Table 1. Regarding
151 the second, slots-for-a-slot, interpretation of the model, we note that the half-life of PSD-95 residing
152 inside the synapse is of the order of 5 hours (*Sturgill et al., 2009*), implying $\beta^{-1} \approx 5 \text{ h} / \ln 2 \approx 7 \text{ h}$.
153 In contrast, the global half-life of PSD-95 has been estimated to be 3.67 days (*Cohen et al., 2013*),
154 implying $\delta^{-1} = 3.67 \text{ d} / \ln 2 \approx 5.30 \text{ d}$. In either case, the assumption of a separation of time scales
155 appears justified.

156 **Competition for Synaptic Building Blocks Induces Multiplicative Scaling**

157 We begin our analysis by finding the stationary solution of the system of coupled differential
158 equations defined by (1) and (2). First, it is convenient to introduce the total number of synaptic
159 slots $S \equiv \sum_i s_i$ and the total number of docked receptors or total synaptic weight $W \equiv \sum_i w_i$ and
160 note that its time derivative is $\dot{W} = \sum_i \dot{w}_i$. This allows us to rewrite (2) as:

$$\dot{p} = -\delta p + \gamma + \beta W - \alpha p(S - W). \quad (3)$$

161 To find the fixed point solution p^∞, w_i^∞ with $W^\infty = \sum_i w_i^\infty$, we set the time derivatives to zero, i.e.,
162 we require $\dot{w}_i = 0 \forall i$ and $\dot{p} = 0$ above. Inserting the first condition into (1) and summing over i yields:

	Value	Description	Reference
β	$(43 \text{ s})^{-1}$	unbinding rate from slots	<i>Henley and Wilkinson (2013, 2016)</i>
δ	$(14 \text{ min})^{-1}$	internalization rate	<i>Ehlers et al. (2007)</i>
ϕ	2.67	relative pool size	M. Renner, personal communication
F	unknown	filling fraction	set by hand to $\{0.5, 0.7, 0.9\}$
γ	unknown	externalization rate	set via (12) to achieve desired ϕ
α	unknown	binding rate to slots	set via (13) to achieve desired F

Table 1. Standard parameters of the model.

163

$$0 = -\beta W^\infty + \alpha p^\infty (S - W^\infty). \quad (4)$$

164 Similarly, setting $\dot{p} = 0$ in (3) gives:

$$0 = -\delta p^\infty + \gamma + \beta W^\infty - \alpha p^\infty (S - W^\infty). \quad (5)$$

165 Adding (4) to (5) then gives the solution for p^∞ :

$$p^\infty = \frac{\gamma}{\delta}, \quad (6)$$

166 The simple and intuitive result is therefore that the total number of receptors in the pool in
 167 the steady state is given by the ratio of the externalization rate γ and the internalization rate δ .
 168 Specifically, the presence of many receptors in the pool requires $\gamma \gg \delta$.

169 We now solve for the steady state solutions w_i^∞ of the w_i by again setting $\dot{w}_i = 0$ in (1) and using
 170 (6) to give:

$$w_i^\infty = \frac{1}{1 + \frac{\beta\delta}{\alpha\gamma}} s_i \equiv F s_i. \quad (7)$$

171 Importantly, we find $w_i^\infty \propto s_i$, i.e. in the steady state the weights of synapses are proportional to
 172 the numbers of slots they have. The constant of proportionality is a *filling fraction* and we denote it
 173 by F . Interestingly, the filling fraction F is independent of the number of receptor slots. Figure 2A
 174 plots F as a function of the ratio of the four rate constants $(\beta\delta)/(\alpha\gamma)$. We refer to this quantity as
 175 the removal ratio, because it indicates the rates of the processes that remove receptors from the
 176 slots relative to the rates of the processes that add them to slots. Note that a filling fraction close to
 177 one requires $\beta\delta \ll \alpha\gamma$.

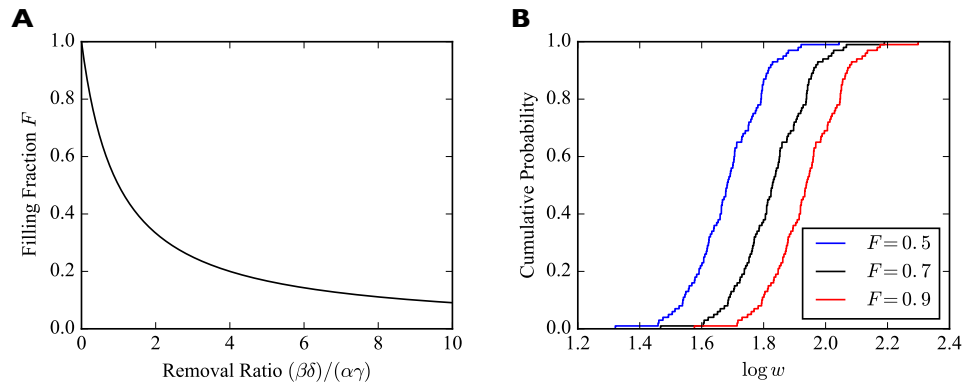


Figure 2. A. Filling fraction F as a function of the removal ratio $(\beta\delta)/(\alpha\gamma)$. **B.** Example empirical cumulative distribution functions (CDFs) of the numbers of receptors bound in individual synapses for fixed numbers of slots drawn from a lognormal distribution and three different filling fractions F . The simulated piece of dendrite has 100 synapses and 100 receptor slots per synapse on average.

178 Summing (7) over i reveals that $W^\infty = FS$, so we can also write:

$$w_i^\infty = \frac{s_i}{S} W^\infty, \quad (8)$$

179 where s_i/S is the relative contribution of synapse i to the total number of slots. Note that if the
 180 filling fraction changes, say, due to an increase in receptor externalization or a change in any of the
 181 other parameters, the *relative* strength of two synapses in the steady state is unaffected:

$$\frac{w_i^\infty}{w_j^\infty} = \frac{s_i}{s_j} = \text{const.} \quad (9)$$

182 Therefore, all synaptic efficacies will be scaled multiplicatively by the same factor.

183 Thus, the analysis so far reveals a first prediction of the model (compare Table 2, *Filling Fraction*):
 184 Under basal conditions synapses in the local group have identical filling fractions. A first corollary
 185 from this prediction is that the ratio of two synapses' efficacies in the steady state is given by the
 186 ratio of their numbers of receptor slots. A second corollary from this prediction is that when one
 187 (or more) of the transition rates changes, all synaptic efficacies are scaled multiplicatively.

188 To illustrate the effect of multiplicative scaling of synaptic efficacies, we consider a piece of
 189 dendrite with $N = 100$ afferent synapses. The number of receptor slots s_i in these synapses are
 190 drawn from a lognormal distribution with mean 1.0 and standard deviation 0.2 and subsequently
 191 scaled such that there are 100 slots per synapse on average. We consider three different filling
 192 fractions $F \in \{0.5, 0.7, 0.9\}$. The empirical cumulative distribution functions (CDFs) of the common
 193 (decadic) logarithms of the w_i are shown in Fig. 2A. The horizontal shifting of the empirical CDFs

194 illustrates the multiplicative scaling of the individual synaptic efficacies.

195 The total number of receptors in the system in the steady state R^∞ is given by the sum of the
196 number of receptors in the pool and the number of receptors attached to slots. Combining the
197 above results, we find:

$$R^\infty = p^\infty + W^\infty = p^\infty + FS = \frac{\gamma}{\delta} + \frac{1}{1 + \frac{\beta\delta}{\alpha\gamma}} S . \quad (10)$$

198 In particular, the total number of receptors in the steady state depends on the total number of
199 slots.

200 In the case of AMPARs, the total number of surface receptors, receptor density, or the number
201 of slots per synapse still remain unknown. Moreover, it is likely that those numbers will vary
202 depending on neuron type and developmental state. However, single particle tracking experiments
203 from the laboratory of Antoine Triller performed on mature hippocampal cultured neurons provide
204 valuable insights into the proportion of exocytosed receptors immobilized in dendritic spines in this
205 particular system. Specifically, recent data suggest that 28% of surface AMPARs are immobilized at
206 synapses while the remaining 72% reside in the pool of extrasynaptic receptors (Marianne Renner,
207 personal communication). Since mature hippocampal cultured neurons are known to exhibit
208 homeostatic and long-term plasticity, we decided to use those numbers for our simulations. Thus,
209 we define the relative pool size ϕ as:

$$\phi = \frac{p^\infty}{W^\infty} = \frac{0.72R^\infty}{0.28R^\infty} \approx 2.67 . \quad (11)$$

210 The relative pool size ϕ together with the filling fraction F determine the unknown externalization
211 rate γ and the rate of binding to receptor slots α . Specifically, using $W^\infty = FS$ and $p^\infty = \gamma/\delta$, we find:

212

$$\gamma = \delta p^\infty = \delta FS \phi . \quad (12)$$

213 Furthermore, by combining this with the implicit definition of F from (7) we can solve for α to obtain:

214

$$\alpha = \frac{\beta\delta}{\gamma} \frac{F}{1-F} = \frac{\beta}{\phi S(1-F)} . \quad (13)$$

215 We can identify the term $S(1-F)$ as the total number of empty receptor slots in the system. The
216 intuitive interpretation of the result is therefore that the binding rate α will be big compared to
217 the unbinding rate β if the number of empty slots and the relative pool size are small. Using
218 the definition of ϕ we can also rewrite the expression for the total number of receptors as $R^\infty =$
219 $(1 + \phi)FS$.

Filling Fraction	Synapses in a local group have identical filling fractions in the basal state.
Pool Size	Manipulation of local pool size scales synapses multiplicatively.
Sensitivity	Filling fraction is most sensitive when pool size matches slot numbers.
Heterosynaptic I	High pool size and filling fraction reduce heterosynaptic plasticity.
Heterosynaptic II	Heterosynaptic plasticity is only transient.
Homosynaptic	Pool size and filling fraction modulate homosynaptic plasticity.
Fluctuations	Spontaneous efficacy fluctuations are bigger for small synapses.

Table 2. Summary of model predictions. Further predictions are mentioned in the Discussion.

220 The above results fully describe the system after it had sufficient time to reach its equilibrium. On
 221 a shorter time scale, however, the system may transiently assume different quasi-stationary states,
 222 because receptor addition and removal are slow compared to receptor binding and unbinding to
 223 and from slots. In the following, we consider the short-term behavior of the model on time scales
 224 where the total number of receptors is approximately constant. This will allow us to reveal, among
 225 other things, a transient form of heterosynaptic plasticity.

226 **Fast redistribution of receptors between synapses is multiplicative**

227 To study the redistribution of receptors on a fast time scale, we exploit the fact that the processes
 228 of receptor externalization and internalization are slow compared to the attaching and detaching of
 229 receptors to and from slots. For instance, the time that an AMPAR remains in the cell membrane
 230 is of the order of ten minutes while the time it resides inside the PSD is of the order of half a
 231 minute. A reasonable approximation on short times scales is therefore to neglect the production
 232 and removal terms in (2). In this case, the total number of receptors $R \equiv W + p$ is constant, as can
 233 be seen by removing the $-\delta p$ and $+\gamma$ terms from (2), and adding (1), summed over all i , which gives
 234 $\dot{p} + \dot{W} = \dot{R} = 0$. In the Methods we show that the steady state solution on the fast time scale is then
 235 given by:

$$W^* = \frac{1}{2} (S + R + \rho) - \sqrt{\frac{1}{4} (S + R + \rho)^2 - RS}, \quad (14)$$

236 where we have introduced $\rho \equiv \beta/\alpha$ as a short hand for the ratio of the rates through which receptors
 237 leave and enter the synaptic slots. We define the corresponding short-term steady-state filling
 238 fraction as $F^* = W^*/S$. Importantly, the short-term filling fraction F^* is identical for all synapses. F^*
 239 can also be expressed as a function of the steady state pool size $p^* = R - W^*$ on the fast time scale,

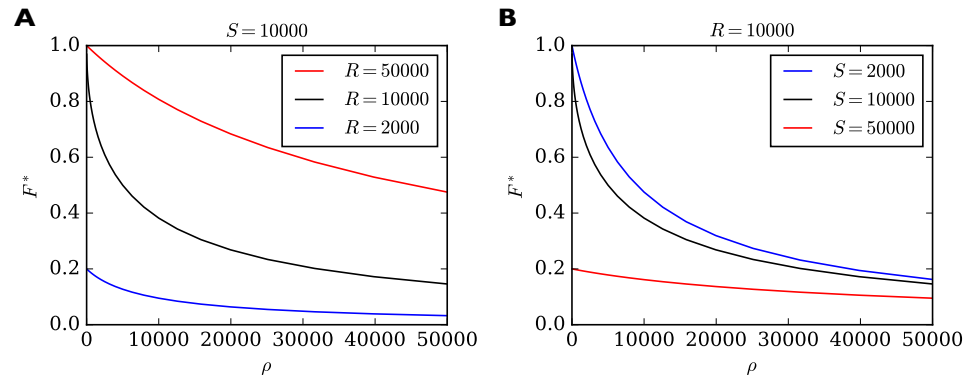


Figure 3. Filling fraction F^* in the short-term approximation of constant receptor number as a function of the ratio of transition rates $\rho = \beta/\alpha$ for different combinations of R and S . **A.** F^* for a fixed number of $S = 10000$ slots and three different receptor numbers as a function of ρ . **B.** For fixed number of $R = 10000$ receptors and three different numbers of slots. Note that F^* reacts particularly sensitively to changes in ρ when ρ is small and when $R = S$ (black curves). In this regime, small changes to, say, the rate of detaching from slots β have a great influence on the filling fraction. In all cases, the shown solution F^* is only transient. Eventually the filling fraction will assume its steady state value F given by (7).

240 leading to a simple expression for the steady state efficacy w_i^* of synapse i on the fast time scale:

$$w_i^* = F^* s_i = \frac{p^*}{p^* + \rho} s_i \quad (15)$$

241 In the full model, this solution is assumed only transiently, because receptors can still enter and
 242 leave the system. If the number of receptors were held constant ($\gamma = 0$ and $\delta = 0$), then F^* , p^* , and
 243 the w_i^* would describe the solution on long time scales.

244 The finding that the short-term steady-state filling fraction is identical for all synapses is analo-
 245 gous to the solution for the long term filling fraction F derived in (7), which is also the same for all
 246 synapses. This implies a second prediction of the model (compare Table 2, *Pool Size*): When the size
 247 of the local receptor pool is manipulated, all synaptic efficacies are scaled multiplicatively.

248 In Fig. 3 we show the behavior of F^* as a function of ρ for different combinations of total number
 249 of slots S and total number of receptors R . For high values of ρ the filling fraction F^* always goes to
 250 zero. For ρ approaching zero, F^* achieves a maximum value which depends on whether there are
 251 fewer or more receptors than slots in the system. If there are more receptors than slots then F^*
 252 approaches one. If there are fewer receptors than slots then F^* approaches the ratio of receptors
 253 to slots in the system. In general, we find that the maximum short-term filling fraction for $\rho \rightarrow 0$ is
 254 given by $F_{\max}^* = \min\{1, R/S\}$. In particular, a high filling fraction can only be achieved if $R > S$, i.e.,

255 there must be more receptors than slots in the system. On the other hand, F^* is most sensitive
256 to changes in ρ when $R = S$. This can be seen by the steep negative slope of the black curves
257 in Fig. 3 for small values of ρ . In fact, for $R = S$ the derivative diverges, i.e., F^* reacts extremely
258 sensitively to changes in ρ (see Methods for details). We therefore note another prediction (compare
259 Table 2, *Sensitivity*): On short time scales the filling fraction reacts most sensitively to changes in
260 binding/unbinding rates if the total number of receptors matches the total number of receptor
261 slots.

262 To illustrate the fast redistribution of receptors, we consider a sudden change in the pool
263 size. In our generic interpretation of the model, this corresponds to the sudden externalization or
264 internalization of AMPARs. To study the effect of such a manipulation, we discretize the full dynamic
265 equations using the Euler method and solve them numerically. For illustration, we consider a piece
266 of dendrite with just three synapses with 40, 60, and 80 slots, whose pool size is changed abruptly
267 (Fig. 4). Parameters are set to achieve a filling fraction of $F = 0.9$ and a relative pool size $\phi = 2.67$.
268 After 2 minutes, the number of receptors in the pool is either doubled (solid lines) or set to zero
269 (dotted lines). In response, all synapses are rapidly scaled up or down multiplicatively. The new
270 equilibrium is only transient, however. On a slower time scale the system returns to its starting
271 point as the slow externalization and internalization processes drive the system back to its steady
272 state solution w_i^∞, p^∞ .

273 The fast equilibration process to a transient steady state also naturally gives rise to a homeostatic
274 form of heterosynaptic plasticity. When, e.g., the number of receptor slots in some synapses is
275 quickly increased, then receptors are redistributed such that the efficacies of synapses with an
276 increased number of receptor slots will grow, while the efficacies of other synapses will shrink, as
277 we discuss in the following.

278 **Competition for receptors induces transient heterosynaptic plasticity**

279 During LTP and LTD, the number of PSD-95 proteins in the synapse, which we assume to form
280 the slots for AMPARs, is increased and decreased, respectively (*Colledge et al., 2003; Lisman and*
281 *Raghavachari, 2006; Ehrlich et al., 2007; Meyer et al., 2014*). Importantly, these changes in slot
282 numbers are mirrored by corresponding adjustments of synaptic AMPAR numbers leading to long
283 lasting changes in synaptic efficacies. This suggests such modifications in AMPAR slot numbers as a
284 central mechanism for memory storage. Therefore, we now investigate how the addition or removal

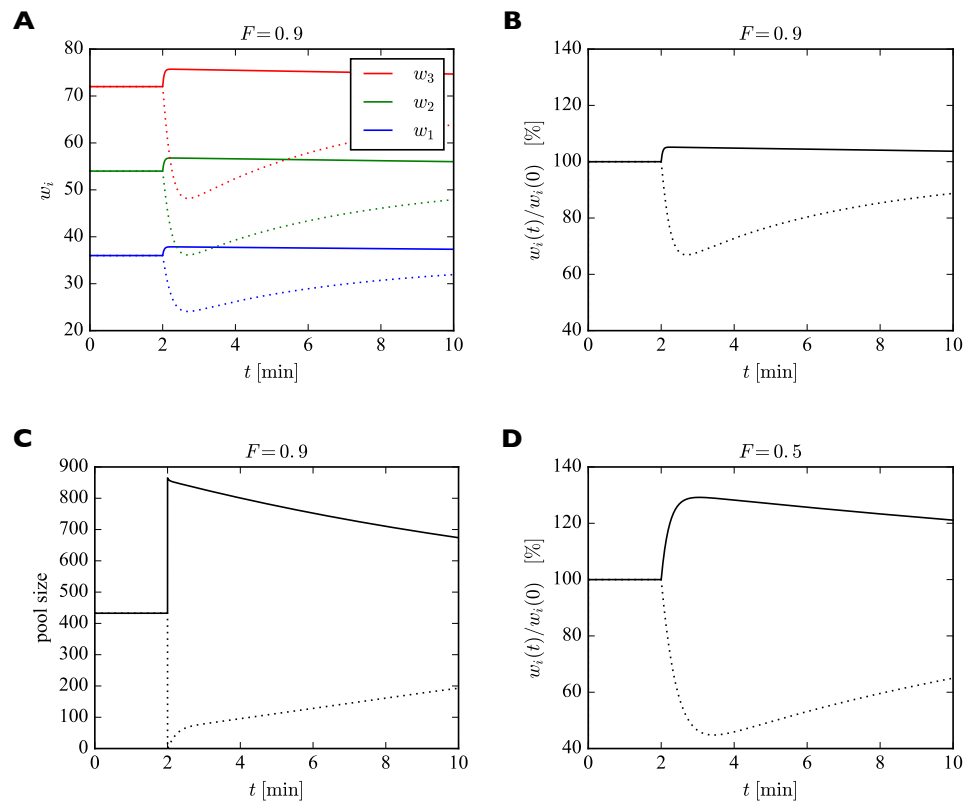


Figure 4. Effect of sudden change of the pool size p on synaptic efficacies. **A.** After 2 minutes, the pool size is either doubled (solid curves) or set to zero (dotted curves). In response, the synaptic efficacies are scaled multiplicatively as receptors are redistributed through the system. Doubling the receptor pool has a relatively weak effect in this example, as the system starts with a high filling fraction of 0.9, meaning that 90% of the slots are already filled at the beginning and there are few empty slots to which the additional receptors can bind. **B.** Same as **A.** but showing relative change in synaptic efficacies, which is identical for all synapses. **C.** Change in pool size. After the sudden increase or decrease in pool size at 2 minutes, there is first a rapid relaxation of the pool size followed by a much slower return towards the original value. **D.** Same as **B.** but for a filling fraction of 1/2. The smaller filling fraction leads to bigger relative changes of the synaptic efficacies. Parameters used were: $\beta = 1/43 \text{ s}^{-1}$, $\delta = 1/14 \text{ min}^{-1}$. The desired relative pool size was set to $\phi = 2.67$. The production rate γ and attachment rate α were calculated according to (12) and (13), respectively.

285 of receptor slots in some synapses alters the efficacies of other synapses in the local group. We find
 286 that the model gives rise to a form of heterosynaptic plasticity, since all synapses are competing for
 287 a limited number of receptors inside the extrasynaptic receptor pool.

288 For illustration purposes we consider a piece of dendrite with four synaptic inputs (Fig. 5). At the
 289 beginning of the simulation, the number of slots in the four synapses are 20, 40, 60, and 80. We
 290 start the system in its steady state with a filling fraction $F^\infty = 0.5$ and a relative pool size of $\phi = 2.67$.

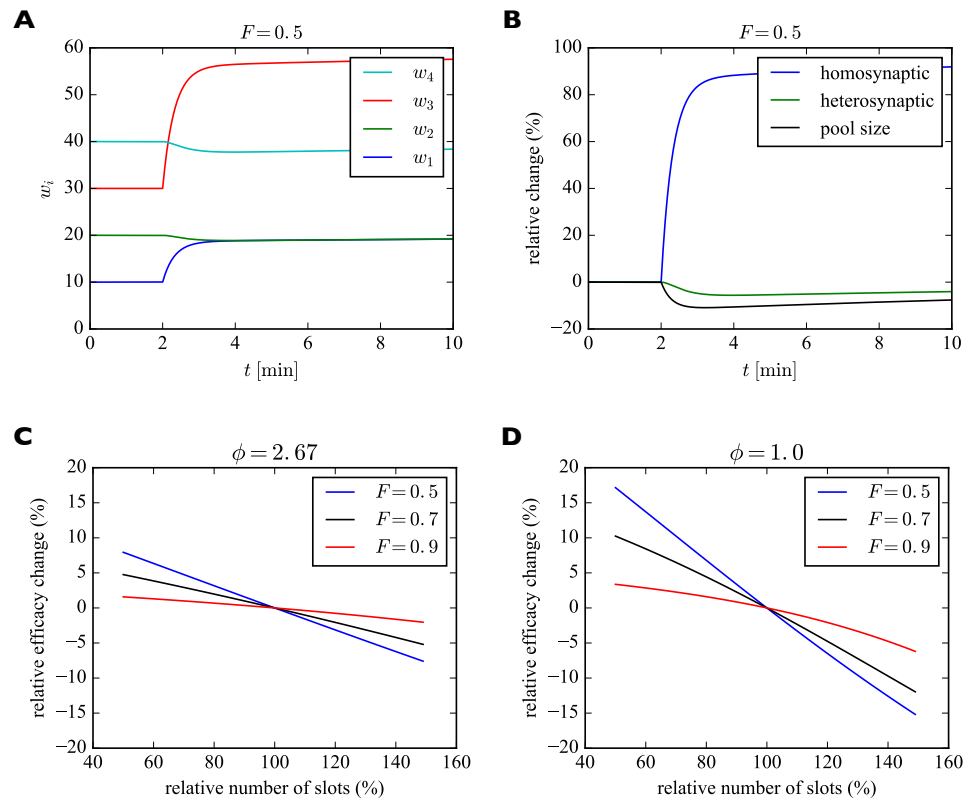


Figure 5. A. Illustration of transient heterosynaptic plasticity. After 2 minutes, the number of slots in synapses 1 and 3 is increased instantaneously. The system quickly reaches a new (transient) equilibrium, where the non-stimulated synapses 2 and 4 are slightly weakened. At the same time, the number of receptors in the pool is reduced. Parameters were: $\beta = 1/43 \text{ s}^{-1}$, $\delta = 1/14 \text{ min}^{-1}$. The filling fraction was set to $F = 0.5$ and the relative pool size was set to $\phi = 2.67$. The production rate γ and attachment rate α were calculated according to (12) and (13), respectively. **B.** Time course of relative changes in synaptic efficacies due to homosynaptic and heterosynaptic plasticity for the experiment from **A**. **C.** Approximate maximum relative change of synaptic efficacy due to heterosynaptic plasticity as a function of the number of receptor slots after homosynaptic plasticity induction for different filling fractions. **D.** Same as **C** but for a smaller relative pool size of $\phi = 1.0$. See text for details.

291 After 2 minutes we instantaneously increase the number of slots in the first (blue) and third (red)
 292 synapse by 100%. Subsequently, the system settles into a new (transient) equilibrium (Fig. 5A).
 293 While w_1 and w_3 increase, the number of receptors in synapses 2 and 4 slightly decrease, although
 294 their numbers of slots have not changed. This behavior corresponds to a form of heterosynaptic
 295 plasticity where synapses grow at the expense of other synapses and is due to the approximately
 296 constant number of receptors on a fast time scale. Note that the sum of synaptic efficacies is
 297 not perfectly constant, however. The increase in synaptic efficacies w_1 and w_3 is bigger than the

298 decrease of synaptic efficacies w_2 and w_4 . The bigger the size of the pool, the stronger is this effect.
299 Close to perfect balancing of synaptic weights would require $p \ll W$. Figure 5B shows the relative
300 changes of efficacies of the synapses undergoing homosynaptic LTP (blue curve corresponding to
301 w_1 and w_3 in A) vs. heterosynaptic LTD (green curve corresponding to w_2 and w_4 in A) and the pool
302 (black curve).

303 What determines the magnitude of the heterosynaptic change? We can calculate this analytically
304 by using the above short-term approximation F^* for constant receptor number. Before plasticity
305 induction, the synaptic efficacy of a synapse in equilibrium is given by $w_i = F s_i = (s_i/S)W$. The
306 induction of homosynaptic plasticity in other synapses changes the total number of available
307 receptor slots and we denote the new number of slots S' . Shortly after homosynaptic plasticity
308 induction the synaptic efficacies of a synapse that did not undergo homosynaptic plasticity will be
309 approximately $w_i^* = F^* s_i = (s_i/S')W^*$ as receptors are redistributed through the system. Therefore,
310 the relative heterosynaptic change of such a synapse is given by $(w_i^* - w_i)/w_i = (F^* - F)/F$ as long
311 as the total number of receptors has not changed much.

312 In Fig. 5C we plot this relative change in synaptic efficacy due to heterosynaptic plasticity as
313 a function of the total number of receptor slots following homosynaptic plasticity induction for
314 different filling fractions. The relative pool size is assumed to be $\phi = 2.67$. First, we can observe
315 that reductions in the total number of slots due to homosynaptic LTD cause heterosynaptic LTP.
316 Conversely, increases in the total number of slots due to homosynaptic LTP cause heterosynaptic
317 LTD. Second, the amount of heterosynaptic plasticity depends on the filling fraction prior to plasticity
318 induction. Specifically, a high filling fraction of 0.9 leads to weaker heterosynaptic plasticity.

319 Figure 5D shows the analogous solution for the case of a smaller receptor pool. Here we set the
320 relative pool size to $\phi = 1.0$. Everything else is identical to Fig. 5C. The scarcely filled pool strongly
321 amplifies the heterosynaptic plasticity effect. When, e.g., new slots are added in this case, the
322 synapses can recruit fewer receptors from the small receptor pool and the heterosynaptic effect on
323 other synapses becomes bigger. A large receptor pool essentially functions as a buffer shielding
324 synapses from heterosynaptic plasticity. Consistent with C, larger filling fractions again lead to less
325 heterosynaptic plasticity.

326 Importantly, these effects are inherently transient. Over a sufficiently long time, the system
327 will settle into a new (true) equilibrium, where every synapse has the same filling fraction F
328 determined by the rate constants $\alpha, \beta, \gamma, \delta$ as described above. The approach towards this new true

329 equilibrium can be seen most easily in Fig. 5B, where the relative change of synaptic efficacy due
330 to heterosynaptic plasticity (green curve) slowly decays towards zero. The new equilibrium will
331 be stable unless the numbers of slots in the synapses change again. In the particular example of
332 Fig. 5A,B, synapses 2 and 4 slowly return to their original efficacies, while synapses 1 and 3 remain
333 permanently strengthened due to their increased number of slots. This effect might explain the
334 often transient nature of heterosynaptic plasticity observed in experiments, e.g., *Abraham and*
335 *Goddard (1983)*.

336 We therefore note the following additional predictions of the model (compare Table 2, *Heterosy-*
337 *naptic Plasticity I, II*): First, the amount of heterosynaptic plasticity is inversely related to the size of
338 the local receptor pool and the filling fraction. Second, heterosynaptic plasticity is only transient.

339 Another mechanism for producing a heterosynaptic effect is changing the transition rates α and
340 β in a synapse-specific fashion. For example, increasing α for some synapses will attract additional
341 receptors to these synapses and lead to a heterosynaptic removal of receptors from the remaining
342 synapses and the receptor pool. A more complete model of homosynaptic LTP that includes a
343 transient synapse-specific change in α and induces heterosynaptic LTD is discussed next.

344 **Time course of homosynaptic LTP and accompanying heterosynaptic LTD**

345 The assumption of a sudden increase in slot numbers from the last section is helpful for mathe-
346 matical analysis but does not reflect biological reality well. Receptor slots need to be trafficked
347 and integrated into the PSD, which cannot happen instantaneously. In fact, modifications in
348 PSD-95 protein number after plasticity induction are known to take several minutes (*Colledge*
349 *et al., 2003; Ehrlich et al., 2007; Meyer et al., 2014*). In general, the induction of LTP is a complex
350 process unfolding across multiple time scales. Here we propose and analyze a more realistic
351 model of homosynaptic LTP and the accompanying heterosynaptic LTD. The model incorporates
352 a synapse-specific transient increase in the insertion rate α of a potentiating synapse and a rapid
353 and pronounced increase of its number of slots followed by a gradual decay back to a sustained
354 elevated level. Thus, both the insertion rates α_i and the slot numbers s_i are now considered a
355 function of time. Formally, in order to do so we replace equations (1) and (2) by:

$$\dot{w}_i(t) = -\beta w_i(t) + \alpha_i(t)p(t) (s_i(t) - w_i(t)) , \quad i = 1, \dots, N \quad (16)$$

$$\dot{p}(t) = -\delta p(t) + \gamma + \sum_i \beta w_i(t) - \sum_i \alpha_i(t)p(t) (s_i(t) - w_i(t)) , \quad (17)$$

356 where we have introduced synapse specific insertion rates α_i and made the time dependence of
357 the various quantities explicit.

358 We model the transient increase in α as a linear increase to four times the original value within
359 17 seconds followed by a linear decrease back to the original value over two minutes. This time
360 course roughly corresponds to the one reported for calcium calmodulin kinase II (CaMKII) activation
361 by Lee and colleagues *Lee et al. (2009)*, essential for LTP induction and maintenance *Malenka et al.*
362 *(1989)*. CaMKII activation leads to the phosphorylation of many synaptic target proteins including
363 the AMPAR auxiliary protein Stargazin which in turn increases the number of stabilized receptors in
364 the synapse *Opazo et al. (2010)*. Thus, we assume here that increased CaMKII activation observed
365 experimentally drives up the insertion rate α . For the time course of the insertion of receptor slots,
366 no direct measurements exist to our knowledge. Therefore, we make the simplifying assumption
367 that the number of slots is related to the change in size of the dendritic spine, which was also
368 measured by Lee and colleagues *Lee et al. (2009)*. We model their data as a sigmoidal increase to
369 five times the original spine volume over the course of two minutes followed by an exponential
370 decay to two times the original spine volume over the course of around twenty minutes (time
371 constant of 5 minutes). We model the change in the number of receptor slots to scale with the
372 $2/3$ power of the change in spine volume, assuming scaling with the surface area rather than the
373 volume of the spine. The filling fraction was set to $F = 0.9$ and the relative pool size to $\phi = 2.67$. The
374 results are shown in Fig. 6.

375 Figure 6 A shows the time course of the relative change of the insertion rate α and the number of
376 receptor slots of the potentiated synapses. Figure 6 B shows the time course of synaptic efficacies.
377 At around 4 minutes the number of slots of the stimulated synapses peaks. Thereafter, the number
378 of slots and the synaptic efficacies of the stimulated synapses decay to their new equilibrium values
379 and the size of the receptor pool slowly recovers. In this example with a high filling fraction of
380 $F = 0.9$ and a relative pool size of $\phi = 2.67$ the heterosynaptic effect is very small. This can also be
381 seen in Fig. 6 C, which shows the relative changes in the synaptic efficacies and the pool size as a
382 function of time. As in the previous section, the amount of heterosynaptic plasticity depends on the
383 filling fraction and the relative size of the receptor pool, however. This is illustrated in Fig. 6D, where
384 we consider a smaller filling fraction of $F = 0.5$ and a smaller relative pool size of $\phi = 1.0$. This leads
385 to a strong depletion of the receptor pool and a large heterosynaptic depression effect.

386 To quantify this effect, we systematically vary the relative pool size ϕ and filling fraction F and

387 observe the peak relative changes in synaptic efficacies during homosynaptic LTP and heterosy-
388 naptic LTD (Fig. 6 E,F). We find that a small pool size strongly reduces the peak homosynaptic
389 LTP and greatly increases the peak heterosynaptic LTD. Furthermore, both homosynaptic LTP and
390 heterosynaptic LTD tend to be reduced by a high filling fraction. These results are consistent with
391 those from Fig. 5.

392 In addition to these already noted effects on heterosynaptic plasticity, this implies another
393 prediction of the model regarding homosynaptic plasticity (compare Table 2, *Homosynaptic*): The
394 amount of short-term homosynaptic plasticity expression is modulated by the pool size and the
395 filling fraction.

396 The changes in efficacies of synapses whose number of receptor slots are unaltered in Figs. 4, 5
397 and 6 are only transient. In the following, we will study the long-term behavior of the model on the
398 time scale associated with receptor externalization and internalization to determine how long it
399 takes for the system to reach its (new) stable fixed point given by w_i^∞ and p^∞ .

400 **Approach to the steady state is governed by externalization and internalization** 401 **rates**

402 To study the system's approach to its long-term steady state we again make use of the separation
403 of time scales argument. Specifically, we assume that the fast dynamics of receptor exchanges
404 between the pool and the synapses quickly reaches its equilibrium before the total number of
405 receptors can change much due to receptor externalization and internalization. For this analysis we
406 return to the original formulation of model. Specifically, the change in the total receptor number
407 from (1) and (2) is approximated by:

$$\dot{R} = \dot{p} + \dot{W} = -\delta p + \gamma \approx -\delta p^* + \gamma, \quad (18)$$

408 where we have replaced the current pool size p with its steady state value $p^*(R) = R - W^*(R)$ for a
409 constant number of receptors in the system. Using $F^*(R) \equiv W^*(R)/S$ we arrive at:

$$\dot{R} = \gamma + \delta F^*(R)S - \delta R. \quad (19)$$

410 For small numbers of receptors in the system, i.e. R close to zero, the steady state filling fraction
411 $F^*(R)$ will be close to zero so that $\dot{R} \approx \gamma$. In contrast, for high numbers of receptors and the filling
412 fraction close to its long-term steady-state value F we find:

$$\frac{1}{\delta} \dot{R} \approx \frac{\gamma}{\delta} + FS - R, \quad (20)$$

F	α [min^{-1}]	γ [min^{-1}]	scale factor a	exponent b
0.5	0.0056	12.1	71.4	-0.52
0.7	0.0093	9.4	55.6	-0.51
0.9	0.0278	6.7	31.8	-0.50

Table 3. Fitting results from the stochastic version of the model, cf. Fig. 8 C. The externalization rate γ and the attachment rate of receptors to slots α are set to obtain different filling fractions while maintaining a relative pool size of $\phi = 2.67$. Parameters β and δ are as in Tab. 1. a and b give the parameters of the power law fits.

413 indicating that R will exponentially approach its steady state value of $\gamma/\delta + FS$ with the time constant
414 $1/\delta$. This behavior is illustrated in Fig. 7. The simulated piece of dendrite has a total of 10 000
415 receptor slots and is initialized with different receptor numbers. We plot the numerical solution of
416 (19) for different initial numbers of receptors in the system. For low receptor numbers, the growth
417 rate of R is approximately γ (compare dotted line). For a filling fraction close to its final steady-state
418 value, R exponentially converges to its steady state of $\gamma/\delta + FS$ with time constant δ^{-1} .

419 **Smaller spontaneous synaptic efficacy fluctuations in larger synapses**

420 Our analysis of the differential equation model above is suitable for studying the average behavior of
421 the system for large numbers of receptors. However, small synapses may only have a few receptors
422 inside them and the effects of stochastic fluctuations may become substantial. To quantify the
423 size of such fluctuations of bound receptor numbers we have developed a stochastic version
424 of the model that explicitly simulates the stochastic binding and unbinding, internalization and
425 externalization of individual receptors (see Methods). We use the model to study the fluctuations of
426 synaptic efficacies under basal steady state conditions. This allows us to quantify the size of synaptic
427 efficacy fluctuations due to the fast exchange of AMPARs between synapses and the receptor pool.

428 For illustration, we consider a local group of 7 synapses with 1, 2, 5, 10, 20, 50, and 100 slots,
429 respectively. We quantify the size of fluctuations of synaptic efficacies using the coefficient of
430 variation (CV), which is defined as the standard deviation of the fluctuating number of receptors
431 bound inside a synapse divided by the time average of the number of receptors bound inside this
432 synapse. A high CV indicates strong relative fluctuations of the synapse's efficacy.

433 Figure 8 A shows the numbers of receptors bound in each synapse as a function of time in one
434 example simulation of 10 minutes. Parameters are as given in Table 1 with the filling fraction set to

relative pool size ϕ	γ [min^{-1}]	F	scale factor a	exponent b
1.0	2.67	0.20	92.6	-0.54
2.67	25.1	0.7	55.4	-0.51
5.0	56.4	0.84	39.1	-0.50

Table 4. Fitting results from the stochastic version of the model, cf. Fig. 8 D. The attachment rate of receptors to slots is chosen as $\alpha = 0.0093 \text{ min}^{-1}$ to obtain a filling fraction of 0.7 for a relative pool size of $\phi = 2.67$. Parameters β and δ are as in Tab. 1. γ is varied to obtain different relative pool sizes ϕ and filling fractions F .

435 $F = 0.5$ and the relative pool size set to $\phi = 2.67$. Figure 8 B shows an example for a much higher
 436 filling fraction of $F = 0.9$. Fluctuations are greatly attenuated.

437 Figure 8 C plots the logarithm of the CV of the number of receptors as a function of the logarithm
 438 of the average number of receptors per synapse, which is given by the product of the theoretical
 439 filling fraction F and the number of receptor slots s_i of the synapse i . Data are shown for three
 440 different filling fractions obtained by increasing α , the rate of receptors binding to receptor slots,
 441 while setting γ to maintain a constant relative pool size of $\phi = 2.67$. The linear relationships evident
 442 in the log-log plot indicate a power law scaling. We fit power law functions of the form $\text{CV} = a(Fs)^b$
 443 to the data (solid lines). Parameters of the fits are given in Table 4 and indicate slopes of around
 444 $-1/2$, i.e. the CV declines approximately with one over the square root of the average number of
 445 bound receptors. Specifically, small synapses exhibit substantial fluctuations of their efficacies with
 446 CVs of up to 100%, while fluctuations are greatly attenuated in strong synapses. For different filling
 447 fractions, the curves are shifted vertically, such that fluctuations are particularly strong for a filling
 448 fraction of 0.5 and are reduced for higher filling fractions.

449 Figure 8 D considers the case where the rates α, β, δ are held constant and the externalization
 450 rate γ is varied to achieve different relative pool sizes $\phi \in \{1.0, 2.67, 5.0\}$. Specifically, to achieve a
 451 specific relative pool size ϕ we set:

$$\gamma = \delta \left(S\phi - \frac{\beta}{\alpha} \right). \quad (21)$$

452 The change in γ also leads to different filling fractions in the three cases, see (7). The results in Fig. 8
 453 D show that an increased pool size will dampen spontaneous fluctuations of synaptic efficacies,
 454 while a reduced pool size promotes stronger fluctuations. We again fit power law functions to
 455 the data. Parameters of the fits are given in Table 4. Taken together, these results imply another

456 prediction of the model (compare Table 2, *Fluctuations*): Small synapses undergo relatively larger
457 spontaneous efficacy fluctuations, which are attenuated by a large pool size.

458 In conclusion, the spontaneous exchange of synaptic building blocks between synapses and
459 dendritic pool leads to substantial fluctuations in synaptic efficacies. This finding is reminiscent of
460 the surprisingly large spontaneous fluctuations in spine sizes in the absence of activity-dependent
461 synaptic plasticity observed recently (*Dvorkin and Ziv, 2016; Shomar et al., 2017; Ziv and Brenner,*
462 *2017*).

463 Discussion

464 The detailed molecular mechanisms underlying different forms of synaptic plasticity are complex.
465 Recent years have seen enormous progress in identifying many of the relevant molecules and
466 signaling pathways. This rapid development is in stark contrast to the simplistic and often purely
467 phenomenological descriptions of synaptic plasticity used in most neural network models. While
468 highly simplified mathematical models have been essential for relating synaptic plasticity “rules”
469 to learning processes at the network level, a full understanding of synaptic plasticity requires the
470 development of more elaborate models that do justice to the complexities of synaptic plasticity at
471 the molecular scale (*Bhalla, 2011, 2014; Tsodyks et al., 1998; Urakubo et al., 2008*). Here we have
472 taken a step in this direction.

473 Hebbian learning tends to lead to runaway growth of synaptic efficacies if not counteracted
474 by competitive or homeostatic mechanisms. To be effective, these compensatory mechanisms
475 must act fast enough so they can catch up with changes induced by Hebbian learning (*Zenke et al.,*
476 *2013; Chistiakova et al., 2015*). Prominent candidate mechanisms are synaptic normalization and
477 heterosynaptic plasticity (*Lynch et al., 1977*). The idea has a long history. Synapses on the dendritic
478 tree compete for a limited supply of synaptic building blocks such that when some synapses grow,
479 they have to do so at the expense of other synapses (*Malsburg, 1973; Lynch et al., 1977; Antunes*
480 *and Simoes-de Souza, 2018*). However, until recently, the lack of knowledge on the nature and the
481 timescales of the molecular processes taking place at synapses did not allow for realistic modeling
482 of such a competition for synaptic resources. Here we have presented a concrete model with a
483 fast normalization of the efficacies of a neuron’s afferent synapses based on this competition for
484 synaptic resources such as AMPA-type glutamate receptors.

485 Our model makes several contributions. First, it formalizes the idea of a fast synaptic normal-

486 ization based on a competition for dendritic resources in an abstract and analytically tractable
487 model. Second, analysis of the model reveals that under the given assumptions, normalization
488 should act multiplicatively, such that relative strengths of synapses are maintained. Multiplicative
489 normalization rules have been used in neural network models for a long time but usually in an
490 *ad hoc* fashion. Our model supports the idea that a fast multiplicative normalization may in fact
491 be biologically plausible. Third, the model naturally gives rise to a transient form of homeostatic
492 heterosynaptic plasticity where synapses grow in efficacy at the expense of other synapses. Fourth,
493 the model quantifies how the amount of heterosynaptic plasticity depends on the size of the local
494 receptor pool and the filling fraction of receptor slots. It thereby reveals a fundamental trade-off:
495 the smaller the pool of available receptors, the more pronounced the heterosynaptic plasticity.
496 In other words, neurons can limit heterosynaptic plasticity effects, but this comes at the price of
497 having to maintain a big receptor pool. Similarly, the model predicts that a larger receptor pool
498 attenuates spontaneous fluctuations in synaptic efficacies, which are particularly strong for small
499 synapses. In the following we discuss how this prediction and others summarized in Table 2 could
500 be tested.

501 How to test the model's predictions.

502 The first prediction of the model is that synapses in a local group have identical filling fractions,
503 see (7). I.e., under basal conditions the same percentage of receptor slots should be filled in these
504 synapses on average. Testing this prediction requires measuring both the number of receptor
505 slots and the number of filled receptor slots for a local group of individual synapses. This could be
506 achieved using a quantitative superresolution approach such as dual-color direct stochastic optical
507 reconstruction microscopy (dSTORM). For a given dendrite, one would have to quantify the number
508 of AMPARs and PSD-95 proteins in a local group of synapses under basal conditions. Our prediction
509 is that the ratio of AMPARs to PSD-95 proteins should be similar in all the synapses. As a corollary,
510 we predict that the relative efficacies of two synapses from a local group should be identical to their
511 relative slot numbers. Testing this hypothesis requires measuring the slot numbers and synaptic
512 efficacies of two synapses from a local group. Specifically, the efficacies of a group of synapses
513 could initially be measured using local glutamate uncaging. Subsequently the number of PSD-95
514 could be assessed using dSTORM. This second approach seems rather challenging, however, as one
515 would have to find in the fixed sample the exact dendrite and specific spines that were stimulated

516 during live-imaging. A second corollary of the model's first prediction is that if any of the transition
517 rates changes, e.g., the rate at which receptors unbind from receptor slots, the filling fractions
518 and synaptic efficacies are scaled by the same factor. Testing this prediction can be achieved by
519 interventions that alter the transition rates. Activation of CaMKII leads to the phosphorylation of the
520 AMPAR auxiliary subunit Stargazin increasing its affinity to PSD-95 (*Hafner et al., 2015*). Thus one
521 could induce a global activation of CaMKII in the neurons (chemical-LTP), fix the cells immediately
522 after, and perform dual-color dSTORM for PSD-95 proteins and AMPARs. When comparing basal
523 state to chemical-LTP, the ratio of PSD-95 proteins to AMPARs should decrease by the same factor
524 for all synapses.

525 The model's second prediction can be tested in a similar way. We predict that manipulating the
526 size of the local receptor pool leads to a multiplicative rescaling of the efficacies of the local group
527 of synapses. To test this prediction, the size of the local receptor pool has to be altered, e.g., by
528 triggering externalization of additional receptors. This could be achieved by treating neurons with
529 TNF- α for instance (*Zhao et al., 2010*). Subsequently the efficacies of the local group of synapses
530 have to be monitored. These efficacies should scale by the same factor.

531 Another prediction of the model is that the amount of heterosynaptic plasticity is inversely
532 related to the size of the local receptor pool. The most direct way of testing this prediction is to
533 manipulate the local receptor pool as suggested above while inducing homosynaptic plasticity in a
534 subset of synapses and measuring the amount of heterosynaptic plasticity in other synapses of
535 the local group. In fact, this set of experiments could resemble the ones performed by Oh and
536 colleagues but adding a TNF- α condition (*Oh et al., 2015*).

537 The transient nature of heterosynaptic plasticity predicted by the model can be tested more
538 easily. It merely requires the induction of homosynaptic plasticity in a subset of synapses in the
539 local group while monitoring the time course of heterosynaptic plasticity in the remaining synapses.
540 Specifically, the time course of recovery from heterosynaptic plasticity should be close to the
541 internalization rate δ of AMPARs.

542 The model's prediction of an influence of the size of the receptor pool on the expression of
543 homosynaptic plasticity requires manipulating the size of the local receptor pool and subsequently
544 inducing homosynaptic plasticity. For example, the peak change in synaptic efficacy during LTP
545 induction should be bigger when the receptor pool has been increased than when it has been
546 depleted prior to LTP induction.

547 Finally, the model predicts that synapses exhibit spontaneous fluctuations in synaptic efficacies
548 due to the dynamic exchange of receptors with the local receptor pool. It predicts that these
549 fluctuations, as measured by the coefficient of variation (CV), scale approximately as one over the
550 square root of the synapses' average efficacies. Testing this prediction can be achieved by repeated
551 measurements of the synaptic efficacy of single synapses in the absence of any plasticity induction
552 using glutamate uncaging.

553 Dendritic morphology and local production.

554 We have assumed that the basal transition rates for receptors attaching and detaching to and from
555 slots are identical for all synapses and that the receptors are distributed homogeneously inside the
556 pool. These assumptions are essential for the multiplicative behavior of the model. If, in contrast,
557 the distribution of receptors across the dendritic tree were very inhomogeneous, this would, all
558 else being equal, correspond to different pool sizes in different parts of the dendritic tree, leading
559 to different filling fractions across the dendritic tree.

560 Properly distributing synaptic building blocks across the dendritic tree is a formidable task
561 (*Williams et al., 2016*). Specifically, if receptors were only produced at a single site corresponding
562 to the cell nucleus and spreading from this point source according to slow transport processes then
563 one would expect a high concentration of receptors close to the nucleus and a low concentration
564 far away from it. This would, all else being equal, lead to large receptor pools close to the cell
565 nucleus and small receptor pools far away from it. *Earnshaw and Bressloff (2008)* have presented
566 such a model. They consider a long dendrite and diffusion of receptors from the soma along this
567 dendrite leading to a high concentration of receptors close to the soma and a small concentration
568 far away from it. In contrast, our model considers a local piece of dendrite, where the concentration
569 of receptors can be assumed to be approximately constant. Therefore, our model does not attempt
570 to make predictions regarding scaling of synaptic efficacies at the **global** level of a neuron's entire
571 dendritic tree. Earnshaw and Bressloff conclude from their model that "it does not appear possible
572 to obtain a global multiplicative scaling" of synaptic efficacies just by changing reaction rates. This
573 conclusion rests on the fact that the distribution of receptors along their simulated dendrite is
574 inhomogeneous. Specifically, Earnshaw and Bressloff assume that protein synthesis occurs mostly
575 at the soma, which leads to an approximately exponential decay of the concentration of receptors
576 towards the distal end of the dendrite. This assumption failed to be confirmed experimentally

577 and has in fact been contradicted by Tao-Cheng and colleagues who found a homogeneous
578 distribution of AMPARs at the neuron surface along the dendritic arbor of hippocampal cultured
579 neurons *Tao-Cheng et al. (2011)*. Earnshaw and Bressloff also cite a study by *Adesnik et al. (2005)*
580 to support the idea of an inhomogeneous distribution of AMPARs. They used ANQX (a modified
581 version of DNQX) known at that time as an AMPAR antagonist (*Chambers et al., 2004*) to monitor
582 synaptic AMPAR exchange after specific inactivation of the surface population. They measured a
583 significantly slower recovery of AMPAR current in dendrites compared to the somatic region. Thus,
584 they concluded that AMPARs are mainly exocytosed at the somatic extracellular membrane and
585 trafficked distally through lateral diffusion. However, since then DNQX has also been shown to
586 act on kainate and NMDA receptors. Additionally, DNQX effects on AMPARs appear to depend on
587 the composition of AMPAR complexes and in particular the type of auxiliary subunits associated
588 with those receptors (*MacLean and Bowie, 2011; Greger et al., 2017*). Since the concentration of
589 receptors between somatic and dendritic membranes appears to be fairly homogeneous, it might
590 be that the actual composition of the receptors varies between those two compartments. In this
591 case, global multiplicative scaling is to be expected in the model of Earnshaw and Bressloff as
592 well. Hence, we believe that our model using minimal assumptions and being restricted to a single
593 dendritic segment with multiple dendritic spines is in good accordance with the recent literature on
594 AMPAR trafficking.

595 A uniform distribution of synaptic building blocks across the entire dendritic tree could be
596 facilitated by local production of these building blocks across the dendritic tree. Local protein
597 synthesis may therefore be essential for global multiplicative scaling behavior observed in biological
598 experiments (*Turrigiano et al., 1998*). More specifically, AMPAR subunits are transmembrane
599 proteins and therefore are synthesized within the endoplasmic reticulum (ER). Translation of
600 proteins seems to occur in a burst fashion in local “hot spots” (*Katz et al., 2016*). Importantly,
601 however, newly synthesized receptors are not necessarily immediately trafficked to the cell surface
602 and in fact a large fraction are distributed across and maintained inside the ER compartment
603 constituting an intracellular pool of receptors waiting to be exocytosed *Greger et al. (2002)*. Thus, the
604 distribution of receptors in the ER may already be more homogeneous than hot spot synthesization
605 would suggest. Furthermore, once released from the ER into the cytoplasm, fast distribution of
606 receptors along microtubules could lead to a rather homogeneous distribution inside the cytoplasm,
607 from where the receptors would be trafficked to the surface. Thus, bursty translation at hotspots

608 inside the ER may still allow for a homogeneous distribution of receptors at the cell surface.
609 We therefore predict that local production of synaptic building blocks across the dendritic tree
610 contributes to their uniform distribution, which in turn might allow global multiplicative scaling
611 behavior and the maintenance of relative strengths of synapses. This could be tested, for example,
612 by specifically blocking local production of synaptic building blocks, which should make their
613 distribution across the dendritic tree less homogeneous and lead to systematic inhomogeneities in
614 synaptic efficacies across the dendritic tree.

615 In this context it is also interesting to note that at least one form of heterosynaptic plasticity
616 tends to be induced locally (*De Roo et al., 2008; Losonczy et al., 2008; Li et al., 2016b*), i.e., at
617 neighboring synapses. Such local action is readily expected in our model if competition for synaptic
618 building blocks is restricted to a *local* pool such as a section of a dendritic branch, with comparatively
619 slow trafficking of building blocks between adjacent pools.

620 Detailed descriptions of AMPAR trafficking and diffusion.

621 The stochastic version of our model describes individual binding and unbinding events of AMPARs
622 to receptor slots, but it does not describe in detail the paths taken by individual AMPARs during
623 their diffusion in the cell membrane. This is a gross simplification, but it facilitates mathematical
624 analysis. More elaborate models were conceived to describe the movement of individual receptors
625 inside the dendritic branch and the PSD (*Earnshaw and Bressloff, 2006; Czöndör et al., 2012; Li*
626 *et al., 2016a*). Such models can incorporate, e.g., the detailed spine geometry or effects of protein
627 crowding.

628 Control of transition rates.

629 Apart from our experiments on modeling LTP, where we introduced a transient and synapse-
630 specific increase of the rate at which receptors bind to slots, we have kept all transition rates
631 constant throughout this paper. In reality, we expect the various transition rates to be flexibly
632 controlled to allow for robust and efficient functioning of the neuron, allowing it to cope with various
633 perturbations. Indeed, constructing a model to describe these various regulatory processes will be
634 an important challenge for the future. Furthermore, AMPARs can be in different states expected to
635 have different transition rates. Specifically, AMPAR complexes containing various sets of auxiliary
636 subunits are very likely to co-exist at the neuron surface (*Schwenk et al., 2012*). Since only a couple
637 of auxiliary subunits have binding domains for PSD-95, multiple types of AMPARs with different α

638 and β parameters could be considered. These topics are left for future work.

639 Slot production and removal.

640 In future work, it will also be interesting to consider changes to slot numbers in more detail.
641 We simulated increases in slot numbers of individual synapses in the context of LTP. Obviously,
642 however, the building blocks of these “slots” also have to be produced, transported, and inserted
643 into synapses, which could be based on similar mechanisms as we have postulated for receptors.
644 Furthermore, slots are also degraded and have to be replaced. In fact, the alternative interpretation
645 of our model discussed in the beginning of the Results section already describes how PSD-95 slots
646 are produced (or degraded) and bind to (or detach from) slots for these receptor slots (“slots-for-a-
647 slot” interpretation). Future work should aim for a model that more fully describes the interactions
648 of AMPARs (and other types of receptors), various TARPs such as stargazin, MAGUK proteins such as
649 PSD-95, and neuroligins as well as their production and trafficking. Along these lines, it will also be
650 interesting to consider the mechanisms underlying different stages of LTP and LTD in more detail.

651 Modeling slow homeostatic synaptic scaling.

652 The model could also be extended to capture slow homeostatic synaptic scaling processes (*Turri-*
653 *giano et al., 1998; Ibata et al., 2008*). In the simplest case, a sensor for the average neural activity
654 of the neuron would drive the production of receptors and/or slots in a homeostatic fashion, such
655 that if, e.g., the average neural activity falls below a target level or range, then receptor and/or slot
656 production are increased to drive up excitatory synaptic efficacies. Such a model would naturally ex-
657 plain the multiplicative behavior of homeostatic synaptic scaling (*Turrigiano et al., 1998*). Obviously,
658 the activity sensor could also sense the average activity in a local neighborhood through a diffusive
659 mechanism (*Sweeney et al., 2015*). Furthermore, instead of homeostatically regulating firing rates,
660 the amount of afferent drive to the neuron or to the local population could be controlled (*Savin*
661 *et al., 2009*), or even other measures of neural and synaptic activity could be used. Finally, all
662 these ideas are not mutually exclusive. It seems likely that neurons control both their firing rate
663 distributions and their amounts of excitatory and inhibitory afferent drive through a combination
664 of different intrinsic and synaptic plasticity mechanisms on different time scales.

665 Receptor subunit composition.

666 Finally, not all AMPARs are created equal. Depending on the composition of subunits, AMPARs have
667 distinct properties in terms of, e.g., calcium permeability and trafficking (see *Henley and Wilkinson*
668 *(2016)* for a recent review). A more complete model should incorporate the diversity of AMPARs (or
669 even other receptor types) and their properties.

670 Conclusion.

671 In conclusion, our model offers a parsimonious explanation for a transient form of homeostatic
672 heterosynaptic plasticity and fast local synaptic normalization, which it predicts to be multiplicative.
673 It therefore supports the use of such rules in neural network models. The model also reveals a
674 fundamental trade-off between the size of the local receptor pool and the amount of heterosynaptic
675 plasticity. This trade-off is akin to a common logistics problem: how much to produce and store of
676 a particular resource in order to a) minimize production costs and storage space while b) limiting
677 the risk of running out of this resource? Arguably, efficient neural functioning requires solving a
678 plethora of related logistics problems with respect to production, transport, and storage of various
679 “goods” and supply of the necessary energy for all these processes. We feel that the time is ripe
680 for a concerted effort to study individual neurons and the entire nervous system from such a
681 *neurologistics* perspective.

682 **Methods and Materials**

683 **Simulation software**

684 The simulation software was written in Python and is available at:

685 <https://github.com/triesch/synaptic-competition> (*Triesch and Vo, 2018*).

686 Differential equations were discretized with the Euler method.

687 The stochastic version of the model was simulated using the Gillespie algorithm (*Gillespie, 1976*).
688 Stochastic reactions were defined for receptors entering or leaving each of the seven synapses
689 and for being added or removed from the receptor pool. This gave rise to a total of 16 possible
690 “reactions” occurring with different probabilities per unit time depending on the current state of the
691 system, i.e., how many receptors are bound in each synapses and reside in the pool. Stochastic
692 simulations were validated against the differential equation model to verify that their average
693 behavior matched that of the differential equation model in different situations.

694 **Calculation of the short-term filling fraction**

695 We exploit the separation of time scales between fast receptor binding and unbinding from slots
696 and slow externalization and internalization of receptors. On the fast time scale, the processes
697 of internalization and externalization can be ignored. Removing the corresponding terms in (2),
698 we again look for the steady state solution by setting the time derivatives of w_i and p to zero and
699 summing over i . This leads to the following quadratic equation for W^* , the steady state number of
700 bound receptors in the short-term approximation (which must not be confused with the long-term
701 steady state solution W^∞ of the full system):

$$W^{*2} - W^* \left(S + R + \frac{\beta}{\alpha} \right) + RS = 0. \quad (22)$$

702 We introduce $\rho \equiv \beta/\alpha$ as the ratio of the rates through which receptors leave and enter the synaptic
703 slots. Using this, the two solutions of (22) are given by:

$$W_{1,2}^* = \frac{1}{2} (S + R + \rho) \pm \sqrt{\frac{1}{4} (S + R + \rho)^2 - RS}. \quad (23)$$

704 The “+” solution is not biologically meaningful, since it leads to $W^* \geq S$ or $W^* \geq R$ (see Appendix),
705 so that the desired steady state solution of the short-term approximation is given by:

$$W^* \equiv W_2^* = \frac{1}{2} (S + R + \rho) - \sqrt{\frac{1}{4} (S + R + \rho)^2 - RS} \quad (24)$$

706 and the corresponding short-term steady-state filling fraction is $F^* = W^*/S$. In the full system, this
707 solution is assumed only transiently, because receptors can still enter and leave the system. If the
708 number of receptors were held constant, then F^* and W^* would describe the stable solution on
709 long time scales.

710 **Sensitive reaction of the short-term filling fraction to changes in reaction rates**
711 **when number of receptors matches number of slots**

712 We are interested in how the short-term filling fraction F^* changes, when the reaction rates α and β
713 or their ratio $\rho \equiv \beta/\alpha$ change. Formally, we consider the partial derivative of the short-term filling
714 fraction $F^* = W^*/S$ with respect to ρ . Using (24) we find:

$$\frac{\partial F^*}{\partial \rho} = \frac{1}{S} \frac{\partial W^*}{\partial \rho} = \frac{1}{S} \left[\frac{1}{2} - \frac{R + S + \rho}{4\sqrt{\frac{1}{4}(R + S + \rho)^2 - RS}} \right]. \quad (25)$$

715 As can be seen in Fig. 3C,D, the most extreme slope is obtained at $\rho = 0$. There the derivative
716 simplifies to:

$$\frac{\partial F^*}{\partial \rho} \Big|_{\rho=0} = \frac{1}{2S} \left(1 - \frac{R+S}{R-S} \right). \quad (26)$$

717 For $R = S$ the slope diverges, i.e., the short term filling fraction reacts extremely sensitively to small
718 changes in ρ when ρ is close to zero.

719 Acknowledgments

720 We thank Marianne Renner for sharing her unpublished results with us and Christian Tetzlaff, Erin
721 Schuman, and Florence Kleberg for helpful discussions.

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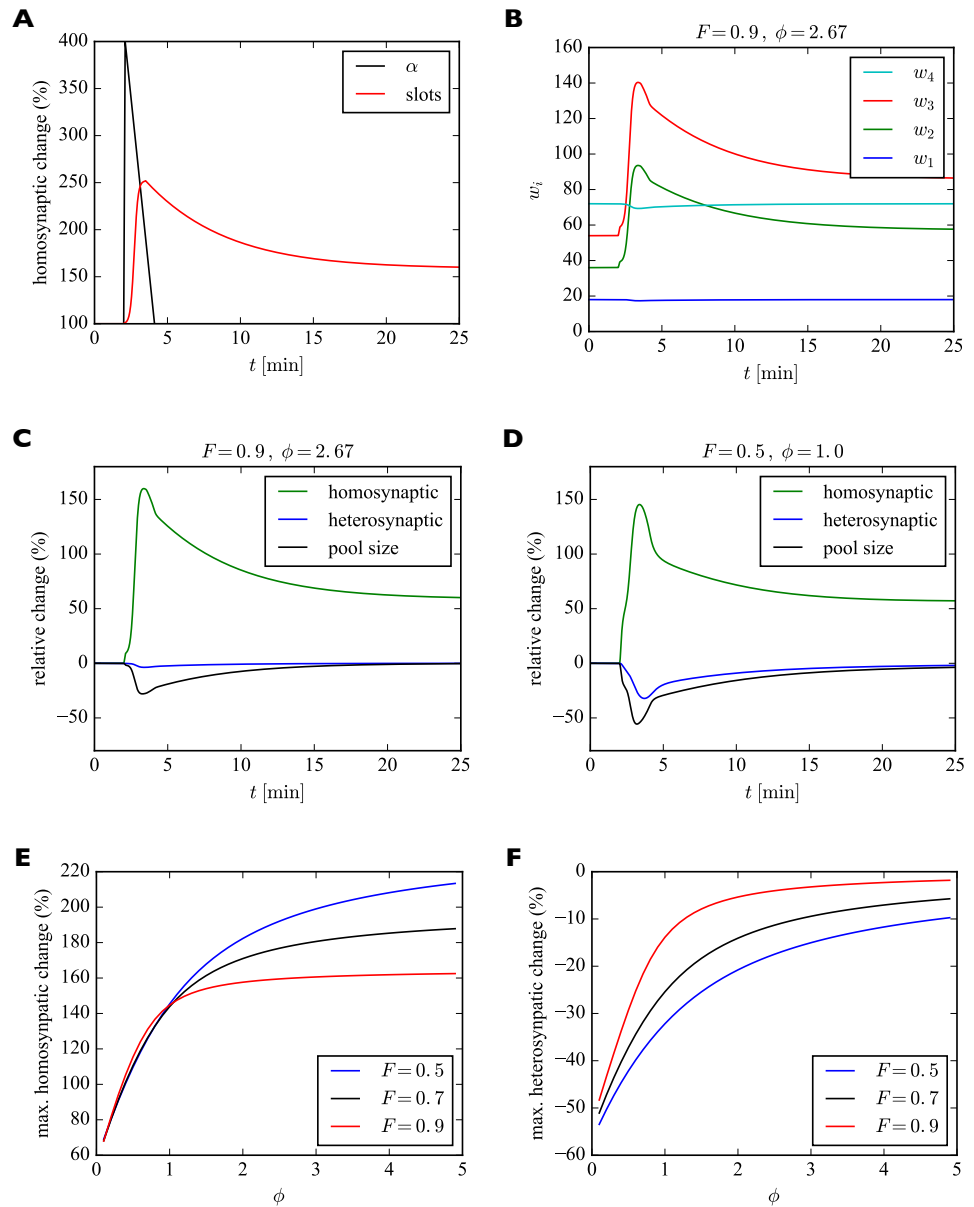


Figure 6. Model of homosynaptic LTP accompanied by heterosynaptic LTD. After 2 minutes, LTP is induced in synapses 2 and 3. This entails a transient synapse-specific change in the insertion rate α of these synapses and a gradual change in their slot numbers. **A.** Time course of relative change of receptor insertion rate α and slot numbers of stimulated synapses undergoing homosynaptic LTP. **B.** Time course of synaptic efficacies for a filling fraction of $F = 0.9$ and a relative pool size of $\phi = 2.67$. Only a very small amount of heterosynaptic LTD can be observed in unstimulated synapses 1 and 4. **C.** Relative change of synaptic efficacies and pool size due to homosynaptic LTP and heterosynaptic LTD in **B** as a function of time. **D.** Same as **C** but for a smaller filling fraction of $F = 0.5$ and a smaller relative pool size of $\phi = 1.0$. Note the smaller transient increase in efficacy of potentiated synapses (compare peaks of green curves in **C** and **D**) and the increased amount of heterosynaptic LTD (compare troughs of blue curves). **E, F.** Maximum amount of homosynaptic LTP (**E**) and heterosynaptic LTD (**F**) as a function of relative pool size ϕ for three different filling fractions.

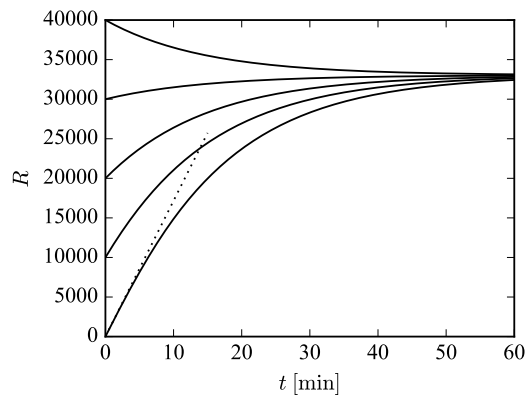


Figure 7. Illustration of long-term behavior under the separation of time scales assumption. Parameters were: $\beta = 1/43 \text{ s}^{-1}$, $\delta = 1/14 \text{ min}^{-1}$. The desired relative pool size was set to $\phi = 2.67$ and the desired filling fraction to $F = 0.9$. The production rate γ and attachment rate α were calculated according to (12) and (13), respectively. The steady-state total number of receptors in this example is given by $R^\infty = (1 + \phi)FS = 33\,030$.

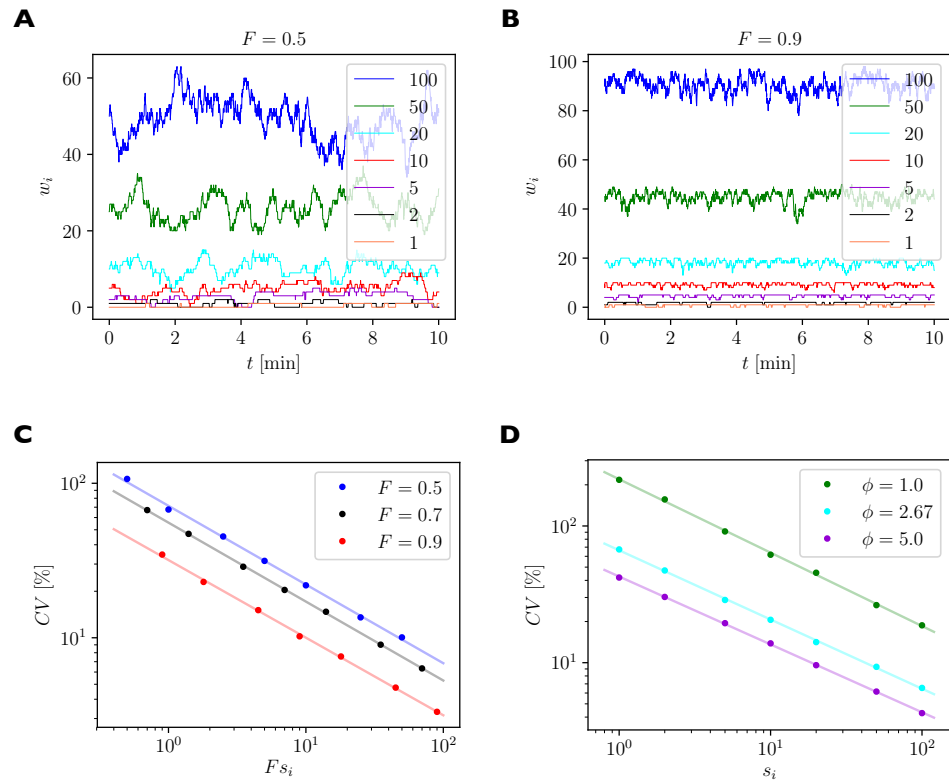


Figure 8. Quantification of spontaneous synaptic efficacy fluctuations due to the fast exchange of receptors between synapses and the receptor pool. **A.** Example simulation of a piece of dendrite with 7 synapses during 10 minutes of simulated time. The number of receptor slots in each synapse is given in the legend. The relative pool size was set to $\phi = 2.67$ and the filling fraction was set to $F = 0.5$ by choosing the binding rate to receptor slots α via eq. 13. **B.** Same as A. but for a higher filling fraction of $F = 0.9$. **C.** Size of synaptic efficacy fluctuations as measured by the coefficient of variation (CV) as a function of the steady state number of receptors in each synapse, which is given by the product of the filling fraction F and the number of slots s_i in synapse i . The relative pool size was set to $\phi = 2.67$. Data points represent averages over 10 simulations of 30 minutes simulated time each. Lines represent linear fits through the data points in double log space. **D.** CV as a function of steady state number of receptors for different relative pool sizes ϕ achieved by holding the binding rate to receptor slots α fixed and varying the externalization rate γ .

877

874 Appendix 1

878

879

875 **The “+” solution from (23) is not biologically meaningful.**

880

881 We show that the “+” solution from (23) is not biologically meaningful. To see this, first note
882 that $W_1 \leq W_2$. Furthermore, any meaningful solution W must fulfill $W \leq R$ and $W \leq S$, i.e.,
883 the number of receptors bound to slots cannot be bigger than the total number of receptors
884 or the total number of slots. If the smaller solution W_1 does not meet both criteria, then
885 the larger W_2 cannot meet them either. So we assume in the following that W_1 meets both
886 these criteria so that $W_1 \leq \min\{R, S\}$. Our argument uses Vieta's formulas for the quadratic
887 equation (22):

888

$$W_1 + W_2 = R + S + \rho \quad \text{and} \quad W_1 W_2 = RS .$$

889

Using the second formula we can write:

890

$$RS = W_1 W_2 \leq \min\{R, S\} W_2 ,$$

891

from which follows that:

892

893

$$W_2 \geq \frac{RS}{\min\{R, S\}} .$$

894

In the case that $R > S$, this leads to $W_2 \geq R$. The only biologically meaningful solution to this
895 is the equality $W_2 = R$. This is the extreme case where all receptors are bound in slots and
896 no receptors remain in the pool. With Vieta's second formula we see that in this case $W_1 = S$.
897 Plugging both results into Vieta's first formula, we see that this solution requires $\rho = 0$, which
898 in turn requires $\beta = 0$. In this case, no receptors would ever leave synapses.

899

The case $R < S$ leads to $W_2 \geq S$. The only biologically meaningful solution to this is the
900 equality $W_2 = S$. This is the extreme case where all slots are filled with receptors. Using
901 Vieta's formulas again leads to the uninteresting requirement $\rho = 0$ for this solution.

902

903 Finally, the case $R = S$ leads to $R = S = W_1 = W_2$ and also requires $\rho = 0$. In summary,
904 the “+” solution in (23) only admits the extreme solutions $W = S$ or $W = R$ requiring $\rho = 0$
(and therefore $\beta = 0$), which are not biologically meaningful.