Modeling Synaptic Dynamics Driven by Receptor Lateral Diffusion

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ABSTRACT The synaptic weight between a pre- and a postsynaptic neuron depends in part on the number of postsynaptic receptors. On the surface of neurons, receptors traffic by random motion in and out from a microstructure called the postsynaptic density (PSD). In the PSD, receptors can be stabilized at the membrane when they bind to scaffolding proteins. We propose a mathematical model to compute the postsynaptic counterpart of the synaptic weight based on receptor trafficking. We take into account the receptor fluxes at the PSD, which can be regulated by neuronal activity, and the interactions of receptors with the scaffolding molecules. Using a Markovian approach, we estimate the mean and the fluctuations of the number of bound receptors. When the number of receptors is large, a deterministic system is also derived. Moreover, these equations can be used, for example, to fit fluorescence-recovery-after-photobleaching experiments to determine, in living neurons, the chemical binding constants for the receptors/scaffolding molecules interaction at synapses.

INTRODUCTION

When a chemical synapse is functional, the information carried by a train of action potentials coming from a presynaptic neuron is transformed into a chemical signal that modulates the membrane potential of the postsynaptic neuron. On the postsynaptic side, the postsynaptic differentiation is organized as a microdomain (1), which contains various types of molecules, all of them constantly renewed with timescales ranging from minutes to hours (2). Recently it has been observed that both excitatory and inhibitory receptors (1,2) are constantly moving in the plane of the plasma membrane and are transiently trapped by scaffolding molecules. Despite these movements, it is unclear how the synaptic weight can be stable. To address this question, we study from a theoretical point of view, the molecular mechanisms involved in receptor trafficking and investigate how the averaged number of receptors at synapses can be maintained constant. In particular, if large fluctuations in synaptic weight are a dominant process then a reliable synaptic transmission could not be ensured. Yet, receptors traffic continuously outside and within synapses and their movements on the neuronal surface can be modeled as random Brownian motion (3). Inside the synaptic area, a receptor can bind to scaffolding proteins, located in the postsynaptic density (PSD) facing the presynaptic terminal (see Fig. 1), which affect its dynamics. Finally, the number of receptors at synapses is regulated by several factors such as the fluxes at the PSD, the interactions with the scaffolding molecules, and the mean time it takes for a free receptor to exit the PSD. In addition, all these factors may be modulated by neuronal activity.

In previous models of synaptic dynamics, transmission was studied in correlation with calcium concentration (4–6). Recently, a mechanism of stabilization has been added to those models to account for synaptic homeostasis (6). In a different context (7,8), fluorescence recovery after photobleaching (FRAP) experiments, where fluorescent molecules are bleached in a given region, was used to study receptor trafficking. We emphasize that the recovery rate provides information on receptor trafficking and it is controlled by diffusion and chemical reactions, in a region which contains obstacles.

We present here a theoretical approach that includes diffusion and binding in a confined environment, when the number of receptors can be small. The model is based on a minimal number of assumptions, used to derive a mathematical expression of the synaptic weight as a function of the number of moving receptors in the PSD. The proposed model is generic and applicable to both excitatory and inhibitory synapses. In particular, we provide at steady state an explicit computation of the synaptic weight, when there is a small and a large number of scaffolding molecules. We obtain an estimate of the mean and variance of the number of bound receptors in terms of inward flux of receptors. This model can be used to interpret FRAP experiments and to estimate the values of chemical constants of the receptor/scaffolding molecule interactions at synapses. Finally we estimate quantitatively various mechanisms involved in regulating the number of receptors inside the PSD.

MATERIALS AND METHODS

The methods of the mathematical derivations are based on stochastic analysis and Markov chain. The simulations are made with MatLab (The MathWorks, Natick, MA).

RESULTS

Theory of receptor trafficking at a single synapse

The postsynaptic density (PSD) is a well-organized microstructure and in the plane of the plasma membrane, it can be

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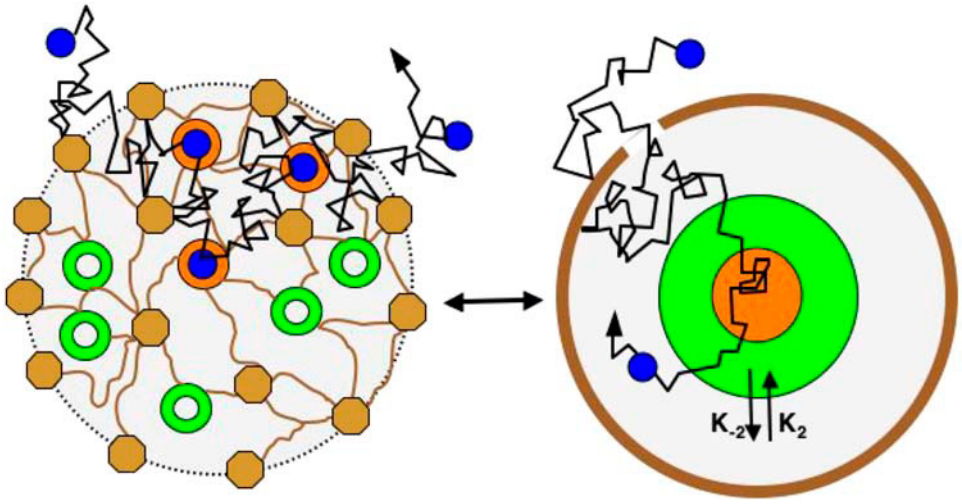

FIGURE 1 Schematic representation of a PSD domain (*right*) containing free (*green*) and bound (*orange*) scaffolding molecules and many other structures such as transmembrane molecules, submembranous-cytoskeleton constituting obstacles, and fences (*brown*). Geometrical organization equivalent to the PSD domain (*right*) with three compartments: the central region contain two interaction states corresponding to bound (*orange*) or unbound (*green*) scaffold molecules to receptors. The total number of scaffolding molecules (*orange plus green*) is constant, but the proportion of bound and unbound depends on the number of receptors in the PSD. Receptors diffuse freely in the peripheral region (*gray*). It is delimited by an equivalent boundary (*brown*) corresponding to obstacles and fences and it is connected to the extrasynaptic region through a small hole that restricts the dynamics of the receptors. A random trajectory of a receptor (*blue*) has been drawn in both pictures (*dashed black line*). The value K_1 is the forward binding rate of a receptor to the scaffolding molecules (which depends on the total number of scaffolding molecules and the mean time it takes to enter this domain); K_{-1} is the backward binding rate.

considered as a two-dimensional geometrical bounded domain Ω with many small holes. It contains scaffolding molecules which transiently bind to the receptors and can modify their biophysical properties. The postsynaptic domain also contains other types of molecules such as adhesion molecules, kinases, actin filaments, and many others (1). Transmembrane molecules such as the one involved in adhesion or bound receptors may act as pickets and submembranous molecules can create a fence (9). To develop the present model, we approximate the complex organization of the PSD by a homogeneous domain containing only two compartments (see Fig. 1):

1. An internal disk, which represents an abstract compartment where receptors are either free or bound to scaffolding molecules; and
2. Around the disk, an annulus—which models the effects of remaining scattered molecules, and does not bind the receptors but restricts their movements (pickets and fences).

The homogeneous domain is limited by a smooth boundary with a small opening, through which receptors can be exchanged with the extrasynaptic region. This homogenization procedure transforms a set of scattered scaffolding molecules inside the PSD into a small domain, modeled as a disk. Moreover, each time a receptor enters this disk, a chemical interaction can occur with a scaffolding molecule. Altogether, this model accounts for:

1. Binding to scaffolding molecules.
2. The presence of obstacles to diffusion.
3. The notion that the postsynaptic density is a geometrically confined microstructure.

In this two-compartment model, the synaptic weight $w(t)$ is the sum of two terms $w(t) = w_1(t) + w_2(t)$. The first term corresponds to permanently anchored receptors coming directly from intracellular pools (10) and does not depend on receptor trafficking on the membrane. The second term w_2 accounts for surface extrasynaptic receptors that can bind to and dissociate from scaffolding molecules.

Markovian equations of receptor dynamics at a synapse

At a molecular level, receptor movements and molecular interactions are dominated by stochastic events. Therefore, when a few (<15) receptors are involved, we use a Markovian model (11) to describe their behavior in synaptic domains. This Markovian model is adapted here to estimate the mean and variance of bound receptors. The dynamics of receptors are characterized by two independent processes:

1. Entrance/exit of receptors in the PSD, modeled by the influx/outflux.
2. Receptor-scaffolding molecule binding/unbinding, modeled by using the on- and off-rate chemical constants.

We denote by R the number of free (unbound) receptors at the synapse and by S the number of free scaffolding molecules (binding sites). The total number of scaffolding molecules in the PSD is denoted S_0.

To derive a dynamical system for R and S, we consider during time t and $t+dt$, the variation of the number of receptors in the homogeneous approximation of the PSD. The variation results from several events:

1. Receptors enter the synaptic region and the inward flux is denoted by $J_{\text{in}}(t)$.
2. Receptors escape the synapse at a rate $\frac{1}{\tau_1}$, where τ_1 is the mean first passage time of a receptor through a small opening, located on the boundary of the PSD. The value

τ_1 has been estimated in Holcman and Schuss (12) and has the asymptotic expression $\tau_1 = (|\Omega|/D\pi)\ln\frac{1}{\varepsilon}+o(1)$, where $|\Omega|$ is the free surface available at the synapse and $\varepsilon = (|\partial\Omega_a|/|\partial\Omega|)$is the ratio of the absorbing part to the total boundary length. By definition, $|\Omega| = |\Omega_0 - \beta[S_0 - S]|$, where $|\Omega_0|$ is the volume of the PSD, S is the number of free scaffolding molecules, and $\beta[S_0 - S]$ is the volume occupied by the bound scaffolding molecules (β is the surface occupied by a single scaffolding molecule). When no receptors are bound, $S = S_0$.

3. A receptor can bind a free scaffolding molecule, according to the standard law of chemical reactions, with a rate k_2RS.
4. A receptor can dissociate from a scaffolding molecule at a rate $k_{-2}(S_0 - S)$.

We assume that the total number of extrasynaptic receptors is large enough compared to the number of synaptic receptors (2,13), so that the influx law can be approximated by a constant. The value of the influx is denoted by $\langle J_{in}\rangle$ and the probability density function that describes the entrance of extrasynaptic receptors is approximated by a Poisson process, where the mean rate is $\langle J_{in}\rangle$. We also approximate receptor association and dissociation from scaffolding molecules by a Poisson process. Using the previous assumptions, the main sources of fluctuations of bound receptors are due to the fluctuations in the receptors entering/leaving the PSD, and to the intrinsic fluctuations associated with chemical reactions.

Derivation of the Markovian equations

To derive an equation for the mean number $N(t)$ of bound receptors at the PSD, we use the conditional probability $p_k(t|q) = \Pr\{N(t) = k|N_{tot}(t) = q\}$ that there are exactly k bound receptors located inside the PSD at time t, given that the total number of receptors inside the synapse is exactly q. The relative position of the scaffolding proteins is disregarded inside the PSD. When we neglect the size of the scaffolding molecules in the expression of Ω_0, the expression of the mean time τ_1 becomes $\tau_1 \approx (|\Omega_0|/D\pi)\ln\frac{1}{\varepsilon}+o(1)$. The probability that k receptors are bound at time t to a scaffolding molecule is denoted by $p_k(t)$. Finally, we define the probability $Q_q(t)$ that there are exactly q receptors located inside the synapse at time t. The mean and variance of bound receptors at time t are respectively given by

$$\begin{cases} M(t) = \sum\limits_{k=1,..S_0} k p_k(t), \\ \sigma^2(t) = \sum\limits_{k=1,..S_0} k^2 p_k(t) - M^2(t) \end{cases}. \quad (1)$$

To compute these quantities, we use Bayes' law,

$$M(t) = \sum_{k=1,..S_0} k p_k(t) = \sum_{k=1,..S_0,\ q\geq k} \sum k p_k(t|q) Q_q(t), \quad (2)$$

where $Q_q(t)$ and $p_{q,k}(t)$ are solutions of two master equations. To derive an equation for $Q_q(t)$, we evaluate during the time interval Δt the fluctuations of the number of receptors entering and leaving the PSD. The number of receptors that enters is $\langle J_{in}\rangle\ \Delta t$. To estimate the number of receptors that leave the PSD, we make the approximation that the mean time a receptor is bound is much shorter than the time it takes to exit. The mean exit time τ_1 from a bounded microdomain has been estimated experimentally in Choquet and Triller (1) and analytically in Holcman and Schuss (12): the order of magnitude for τ_1 is tens of seconds, while the backward binding rate between a scaffolding molecule and a receptor is guessed to be at most of the order of few seconds (A. Triller, unpublished data). Moreover, when the amplitude of the receptor influx is large enough, so that there are always free receptors available in the PSD, then the dynamics of entrance/exit can be decoupled from the binding/unbinding. In that case, receptors are always available and the mean and variance of receptors entering into the PSD can be estimated as follows: when $q+1$ receptors are located inside the synapse, the probability that one receptor exits is $(q+1)\frac{\Delta t}{\tau_1}$, which leads to the Markov equation

$$\begin{aligned} \dot{Q}_q(t) &= -\left(\langle J_{in}\rangle + \frac{q}{\tau_1}\right) Q_q(t) + \langle J_{in}\rangle Q_{q-1}(t) \\ &\quad + \frac{q+1}{\tau_1} Q_{q+1}(t), \quad \text{for} \quad q \geq 1 \\ \dot{Q}_0(t) &= -\langle J_{in}\rangle Q_0(t) + \frac{1}{\tau_1} Q_1(t). \end{aligned} \quad (3)$$

We present in the Appendix the set of equations that, in the general case, describe the joint probability of having k bound receptors and a total number of receptors $Q(t) = q$ at time t. The assumption above allows us to neglect the dependence of $Q_q(t)$ on the number k of bound receptors.

To derive the second master equation describing the transition probability $p_k(t|q)$ of having k bound scaffolding molecules, when the total number of receptors is fixed at a value q (no receptors exit the PSD), let us consider the events occurring during the time interval Δt: a receptor can either bind to a free scaffolding molecule or becomes unbound or nothing happens. The probability of unbinding is $k_{-2}k\Delta t$, while the probability of binding is $k_2(q - k)(S_0 - k)\Delta t$. This implies for $q \geq k$ and $S_0 \geq k$ that

$$\begin{aligned} \dot{p}_k(t|q) &= -[k_{-2}k + k_2(q-k)(S_0-k)]p_k(t|q) \\ &\quad + k_{-2}(k+1)p_{k+1}(t|q) \\ &\quad + k_2(q-k+1)(S_0-k+1)p_{k-1}(t|q), \end{aligned} \quad (4)$$

$$\dot{p}_{S_0}(t|q) = -k_{-2}S_0 p_{S_0}(t|q) + k_2(q - S_0 + 1)p_{S_0-1}(t|q), \quad (5)$$

$$\dot{p}_0(t|q) = -(k_2 q S_0)p_0(t|q) + k_{-2}p_1(t|q). \quad (6)$$

When $S_0 \leq k$, $p_k(t|q) = p_{S_0}(t|q)$.

Steady-state solutions

At steady state, the solution of Eq. 3 is given by

$$Q_k = e^{-\tau_1\langle J_{in}\rangle}\frac{1}{k!}(\tau_1\langle J_{in}\rangle)^k, \quad \text{for} \quad k \geq 0. \quad (7)$$

Let $p_k(q)$ denote the steady-state solution of the expressions in Eq. 4. It is

$$p_k(q) = C\frac{1}{k!}\left(\frac{k_2}{k_{-2}}\right)^k \frac{q!}{(q-k)!}\frac{S_0!}{(S_0-k)!} \text{ where } k \le \min(S_0, q), \tag{8}$$

when $q \le S_0, p_{S_0}(q) = C(k_2/k_{-2})^{S_0} q(q-1)..(q-S_0+1)$. For $q \le S_0$, let C be a normalization constant to be computed, then $p_q(q) = C(k_2/k_{-2})^q S_0(S_0-1)..(S_0-q+1)$. To obtain an expression for the mean and the variance of the number of bound receptors at steady state, we use expressions from Eqs. 7 and 8, and the normalization condition imposed by $1 = \sum_{k=0,..S_0} p_k$. If we denote

$$\vartheta = \left(\frac{k_2}{k_{-2}}\langle J_{in}\rangle\tau_1\right), \tag{9}$$

then $C = (1/(1+\vartheta)^{S_0})$. The parameter ϑ reflects both receptors binding and dissociation from the scaffolding molecules and the influx/outflux of receptors in the PSD at equilibrium. The mean and the variance are given by

$$M(\infty) = \sum_{k=1,..S_0} kp_k = \frac{1}{(1+\vartheta)^{S_0}} \sum_{k=1,..S_0} S_0! \frac{\vartheta^k}{(k-1)!(S_0-k)!}, \tag{10}$$

$$\begin{aligned}\sigma^2(\infty) &= \frac{1}{(1+\vartheta)^{S_0}} \sum_{k=1,..S_0} k^2 p_k - \left(\frac{1}{(1+\vartheta)^{S_0}} \sum_{k=1,..S_0} kp_k\right)^2 \\ &= \frac{1}{(1+\vartheta)^{S_0}} \sum_{k=2,..S_0} S_0! \frac{\vartheta^k}{(k-2)!(S_0-k)!} \\ &\quad + M(\infty) - M^2(\infty).\end{aligned} \tag{11}$$

When $\vartheta \ll 1$ is small, the mean number and the steady variance of bound receptors can be approximated by

$$M(\infty) \approx S_0\vartheta,\ \sigma^2(\infty) \approx S_0\vartheta. \tag{12}$$

However, when $\vartheta \gg 1$, $M(\infty) \approx S_0\left(1-\frac{S_0}{\vartheta}\right)$, $\sigma^2(\infty) \approx (S_0^3/\vartheta)$. The graphs of $M(\infty)$ and $\sigma^2(\infty)$ as a function ϑ are given in Fig. 2 for various numbers of scaffolding molecules. When ϑ is large, the mean number of bound receptors converges to the total number of scaffolding molecules. Moreover, the variance has a unique maximum and decays to zero for large ϑ.

This model was derived using the approximation that the binding time constant of a receptor to a scaffolding molecule is shorter than the mean escape time τ_1. The general equations are provided in the Appendix.

Deterministic model of receptor dynamics at a single synapse

When the in- and out-fluxes and the binding-unbinding involve a sufficiently large number of receptors (>15), then the dynamics of the synaptic receptors can be modeled using

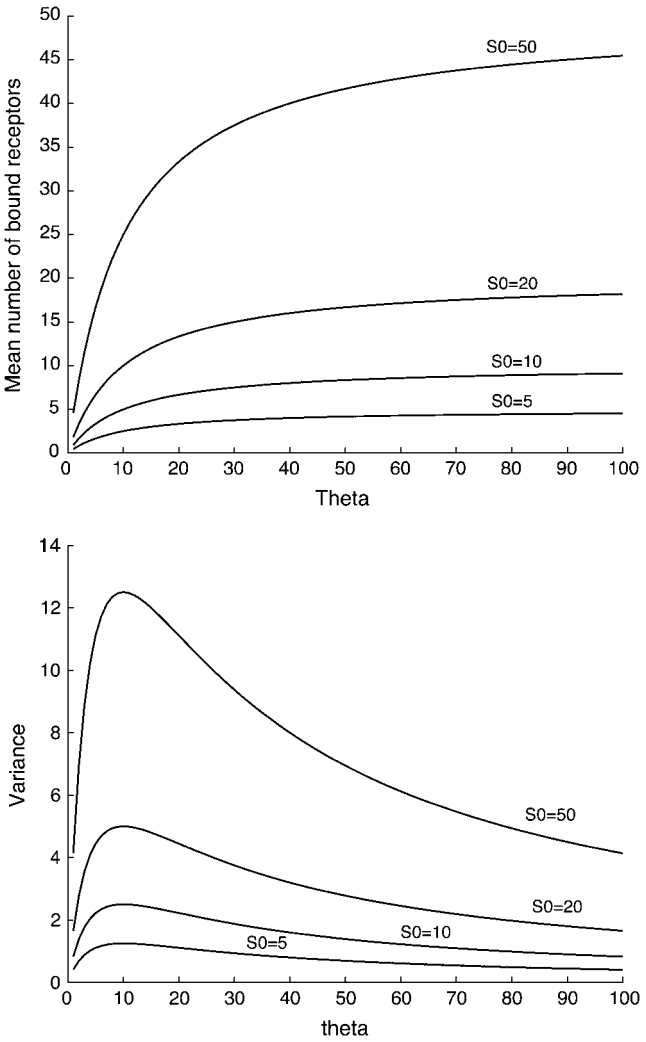

FIGURE 2 Mean and variance of the number of bound receptors at a single synapse. The mean and the variance are plotted as a function of the equilibrium parameter $\vartheta = (k_2/k_{-2})\langle J_{in}\rangle\tau_1$ for various numbers of scaffolding molecules S_0 = 5, 10, 20, 50. When ϑ is large, the variance converges to zero and the mean converges to the total number of scaffolding molecules available. The unit of k_2 and k_{-2} is 1/s. The value k_2 has to be normalized by dividing by the concentration of scaffolding molecules.

the standard differential equations of chemical reactions. To model the dynamics of bound receptors, we use the same notations as in the previous paragraph. Initially the number of free scaffolding molecules is $S(0) = S_0$. The number of bound receptors at time t is by definition $S_0 - S(t)$.

As in the previous paragraph, by analyzing the four possibilities given above, we derive the equations describing the dynamics of receptors. During time t and $t+dt$, the variation in the number of receptors leads to Eq. 13,

$$\frac{dR}{dt} = -\frac{R}{\tau_1} - k_2RS + k_{-2}(S_0 - S) + J_{in}(t), \tag{13}$$

$$\frac{dS}{dt} = -k_2RS + k_{-2}(S_0 - S), \tag{14}$$

while Eq. 14 is simply the dynamics of the chemical reactions with the scaffolding molecules. The value k_2 represents the normalized forward binding rate (the inverse of mean time it takes for a receptor to bind to one of the free scaffolding molecules). In practice, one can obtain this normalized value by dividing the standard forward binding rate by the concentration of scaffolding molecules. The value k_{-2} is the backward binding rate, given in the unit of 1/s.

Remarks

1. Using the previous equation, the first part of the synaptic weight is given by $w_2(t) = \gamma(S_0 - S(t))p(t|V)$, where $p(t|V)$ is the probability that the channel opens, and may depend on the voltage V. The value w_2 is proportional to the number of receptors bound to scaffolding molecules. The conductivity γ can depend on binding to scaffolding molecules. For example, this is the case for AMPA receptors bound to stargazin (14).
2. In the steady-state regime, the inward flux at the synapse J_{in} is time-independent and depends on the concentration of extrasynaptic receptors only. The steady state of Eq. 13 is given by

$$-J_{\text{in}} = -\frac{R}{\tau_1} - k_2 RS + k_{-2}(S_0 - S), \tag{15}$$

$$0 = k_2 RS - k_{-2}(S_0 - S). \tag{16}$$

Thus, the outflux $J_{\text{in}} = \frac{\text{R}}{\tau_1}$ is balanced by the influx. The number of bound receptors is given by

$$(S_0 - S) = \frac{J_{\text{in}} k_2 \tau_1}{J_{\text{in}} k_2 \tau_1 + k_{-2}} S_0. \tag{17}$$

Ultimately the number of scaffolding molecules S_0 determines the total number of receptors present at the PSD.

4. The dynamical system shown in Eqs. 13 and 14 has a unique fixed point, which is an attractor of coordinates $(R_{\text{st}}, S_{\text{st}}) = (J_{\text{in}}\tau_1, (\text{k}_{-2}/\text{J}_{\text{in}}\text{k}_2\tau_1 + \text{k}_{-2})S_0)$. The slowest decay to the equilibrium is characterized by an exponential rate $e^{-\lambda_- \text{t}}$, which is the smallest eigenvalue of the linearized matrix at the fixed point,

$$\lambda_- = \frac{2a}{b + \sqrt{b^2 - 4a\tau_1}},\ a = k_{-2} + J_{\text{in}} k_2 \tau_1 \quad \text{and}$$
$$b = 1 + k_2\tau_1 S_0 + J_{\text{in}} k_2 \tau_1 + \tau_1 k_{-2}.$$

Application: analysis of FRAP experiments

FRAP experiments consist in bleaching tagged receptors in a specific region, such as the PSD, and measuring the time it takes for unbleached receptors to fill the bleached area. The recovery process depends on different molecular events such as the diffusion of unbleached receptors into the PSD, bleached receptors not being bound to a scaffolding molecule and unbleached receptors being bound to the scaffolding molecule.

To model these experiments, the deterministic model in Eqs. 13 and 14 can be modified by including two receptors states: bleached R_{b} and unbleached R_{u}. The value SR_{b} is the number of bleached receptors bound to a scaffolding molecule. The deterministic FRAP equation can be written

$$\begin{cases} \dfrac{dR_{\text{b}}}{dt} = -\dfrac{R_{\text{b}}}{\tau_1} - k_2 R_{\text{b}} S + k_{-2}[SR_{\text{b}}], \\ \dfrac{dR_{\text{u}}}{dt} = -\dfrac{R_{\text{u}}}{\tau_1} - k_2 R_{\text{u}} S + k_{-2}(S_0 - S - SR_{\text{b}}) + J_{\text{in}}, \\ \dfrac{dSR_{\text{b}}}{dt} = k_2[R_{\text{b}}][S] - k_{-2} SR_{\text{b}}, \\ \dfrac{dS}{dt} = -k_2(R_{\text{b}} + R_{\text{u}})S + k_{-2}(S_0 - S), \end{cases} \tag{18}$$

where the notations have been used in the previous paragraph. The first expression in Eq. 18 describes the dynamics of bleached receptors, which can exit the bleached area, bind, or unbind to scaffolding molecules. The second expression in Eq. 18 describes unbleached receptors, which enter with a flux J; they can bind or unbind to scaffolds. (In this equation, we have used the conservation-of-mass equation to obtain that the number of bound unbleached receptors is equal to $S_0 - S - SR_{\text{b}}$.) The third equation in the system above describes the dynamics of expression in the free scaffolding molecules, which can either bind to a bleached or an unbleached receptor. If at time 0, all receptors in the PSD are bleached, then the initial conditions are given by

$$R_{\text{u}}(0) = 0,\ R_{\text{b}}(0) = R_{\text{e}},\ S(0) = S_{\text{e}},\ SR_{\text{b}}(0) = S_0 - S(0),$$

where R, S_{e} are the concentrations at equilibrium. The results of the simulations are given in Fig. 3: bleached receptors escape the PSD and are replaced by unbleached receptors. Due to the different time constants (τ_1, k_2, k_{-2}, J), two timescales at most can emerge: a first timescale given by the constants (τ_1, J) reflects the exchange of receptors with the rest of the plasma membrane, while the second timescale, given by the constants (k_2, k_{-2}) reflects binding to and dissociation from the scaffolding molecules.

The system of equations in Eq. 18 can be used to fit FRAP data after Brownian receptors diffusing in a confined microdomain, where receptors can bind to scaffolding molecules. Indeed, Eq. 18 can be considered as a rough approximation of the standard reaction diffusion equation, in the limit where the ratio of the absorbing to the reflecting part of the boundary of the bleached region is small. Under this assumption, the escape rate of any Brownian receptor becomes exponentially distributed (Poissonian). The reason is that the first eigenvalue associated with the diffusion equation is well separated from the rest of the spectrum and is close to zero. In particular, the system of expressions in Eq. 18 extends previous models, used to fit FRAP experiments (7). When the number of receptors involved is small, instead of the system of equations in Eq. 18, the equations given in

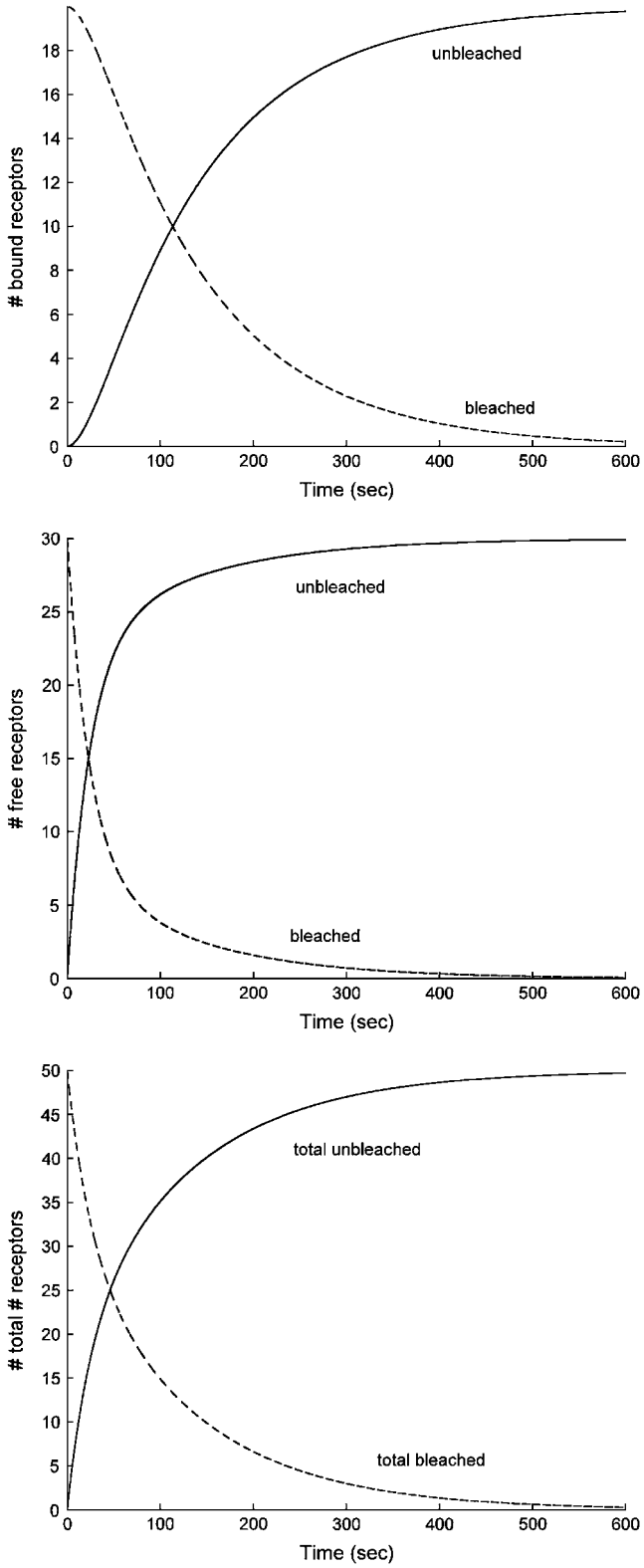

FIGURE 3 Simulations of bleached receptor recovery at PSD. (*Top*) Time-course of bleached receptors bound to the scaffolding molecules. (*Middle*) Time-course of free bleached receptors in the PSD. (*Bottom*) Time-course for the total amount of receptors (bound+unbound). Parameters used: $\tau_1 = 30$ s, $S_0 = 20$ (number of scaffolding molecules), influx $J = 1\ s^{-1}$, and the binding constants $k_2 = 1$ and $k_{-2} = 0.01\ s^{-1}$. Bleached receptors diffuse outside the PSD and are replaced by unbleached ones. Due to the different timescales in the affinity constants, binding to scaffolding molecules takes longer than the process of entering the PSD domain by diffusion.

the Appendix should be used. Fitting a FRAP experiment can be useful to identify one of the four time constants (τ_1, k_2, k_{-2}, J). However, if more than one parameter is missing, then it is not clear that the present approach would give a unique couple of solutions. Let us review the meaning of each parameter: τ_1 depends on the local amount of fence versus local openings, the surface of the microdomain and the free diffusion constant. The flux J depends on the concentration of extrasynaptic receptors, the total opening area, and the mean time it takes for a receptor to enter. These time constants contain complex information about the geometry of the microdomain and may be considered to be unknowns. Although k_{-2} depends on the local potential and can be obtained from biochemical experiments, k_2 depends on the internal structure of the microdomain, making it a difficult parameter to measure. Once the geometry of the microdomain is known, k_2 may be estimated analytically as the flux of the receptors to the binding sites within the PSD. Single particle tracking combined with FRAP experiment should allow to access the parameter k_2.

REGULATION OF RECEPTOR DYNAMICS BY NEURONAL ACTIVITY

Neuronal activity can modulate the number and/or the biophysical properties of receptors in the PSD (17,18). This regulation has been demonstrated in many cases, including the well-known case of synaptic plasticity (17). Another remarkable example of receptor number modulation is homeostatic plasticity, where a change in the mean input activity scales all the synaptic weights in the opposite direction (18). Various factors may modify synaptic weight, such as changing the net flux J_{in} of receptors to the PSD, the open probability or the conductivity of the channels or the number of scaffolding molecules S_0. We propose now to model these changes in terms of receptor regulation moving by lateral diffusion.

Regulating the net flux

Neuronal activity can modulate the geometrical properties of dendritic spines (15,16), which are the locus of excitatory postsynaptic connections. Neuronal activity can also affect the size of the absorbing part of the PSD boundary, which changes the value of the mean exit time τ_1. The molecular mechanisms might involve calcium-dependent processes such as actin polymerization. We will examine now that changing the size of the PSD domain or the length of the

absorbing part of the PSD boundary domain affects the value of the time τ_1 and the outflux.

The geometrical quantities related to the PSD determine the total net flux of receptors, which is the sum of the influx J_{inf} and the outflux J_{outf}. The outflux is given explicitly as $J_{\text{outf}} = (\text{N}_{\text{free}}/\tau_1)$, where N_{free} is the number of free receptors that can exit the PSD per unit of time. The number of extrasynaptic receptors is not much affected by the influx coming from the synapse, because most neuronal receptors are located extrasynaptically (2).

Moreover, the local concentration of extrasynaptic receptors near the PSD could theoretically be modulated due either to a change in the absorbing boundary length of the PSD or to a modulation of the position of endocytotic sites near the PSD. Both events may be controlled indirectly by activity-dependent processes that involve calcium (19). By solving Eq. 17, for various mean exit times of the PSD at equilibrium, the number of bound receptors is plotted as a function of the influx in Fig. 4. When the flux increases to 1/s, almost all PSD receptors are bound.

Finally, in a one-dimensional computation it is possible to estimate the attenuation of the flux due to an absorbing region located near the PSD, when the flux is delivered at a distance L from the PSD (see (11) for details) and we obtain

$$\Phi_{\text{inf}} = \frac{\Phi_{\text{total}}}{1 + CL}, \tag{19}$$

where the total flux is Φ_{total} and C a positive constant.

We conclude at this stage that modulating the geometry of a dendritic spine changes the mean time a receptor enters into the PSD and thus the influx of receptors. A rapid change in spine shapes is thus a fast regulation mechanism of the number of receptors at the PSD.

Moreover, adding endocytosis wells near the periphery of the PSD is likely to affect the receptor influx by modifying the boundary condition for the receptor concentration near the PSD entrance.

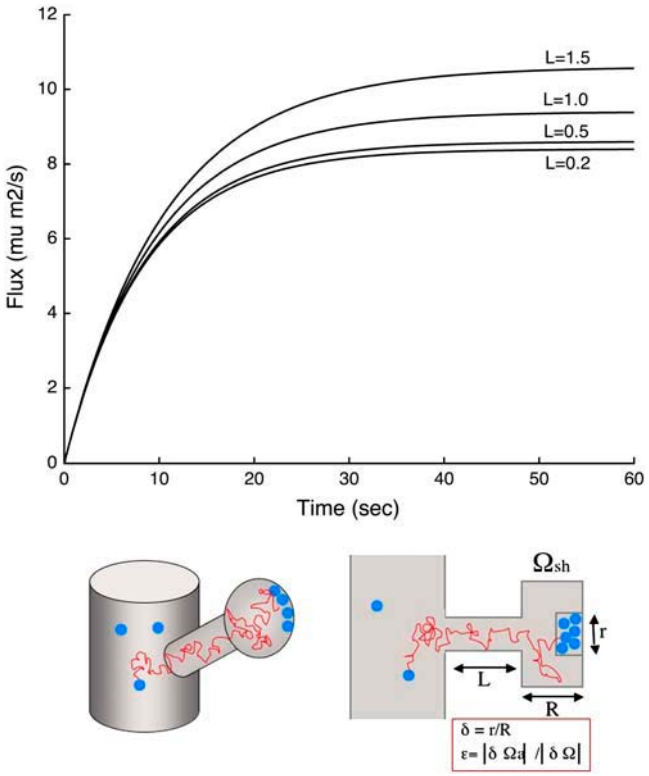

FIGURE 4 Regulation of the receptor influx by spine neck length. (*Top*) Flux recovery after changing spine length. The inward flux of receptors recovers to a steady-state flux, after the spine length is changed to a length L= 0.2, 0.5, 1, and 1.5 μm. The curves of the recovery dynamics are obtained from Eq. 21. The recovery time depends on the square of the length of the spine neck. The simulations are obtained for a receptor density equal to 5 μm^2/s. The characteristic of the PSD and the head is assumed to be $(|\Omega_{\text{sH}}|/2\pi\text{D})(2\ln(1/\varepsilon)+\ln(1/\delta)+3\log 2-(1/2)+o(1))= 4.5$, and the free diffusion constant is $D = 0.1$ μm^2/s. The fluxes reach steady state after a few tens of seconds, when initially the dendritic spine does not contain any receptors. As the spine length increases it takes longer for the flux to reach the steady state. (*Bottom*) Scheme of receptor trafficking on the spine neck. A typical trajectory is shown when the receptor is initially located on the dendrite. The spine neck constitutes a barrier for receptor diffusion and regulates the number of receptors arriving at the PSD, when they are coming from the dendritic shaft.

Dendritic spine geometry regulates the fluxes and controls the number of receptors at the PSD

Due to the difference in the surface area of extrasynaptic and synaptic membranes, and despite the higher (10–100 times) concentrations of receptors at synapses, most receptors are located extrasynaptically (2). The case of dendritic spines is particularly interesting since they constitute an open but dynamic compartment where receptors travel from the dendritic shaft to the PSD. To estimate how the dendritic spine geometry affects the flux and ultimately the number of bound receptors at the PSD, we give an explicit expression of the influx at the PSD. We recall that the outflux in the PSD through the spine is by definition the number of receptors per second located in the dendritic shaft traveling to the PSD (the schematic representation is given in Fig. 5, *bottom*). The flux depends on the spine geometry: If C_{den} denotes the concentration of receptors in the dendrite, and $\tau_{\text{D–S}}$ is the mean time it takes for a receptor to arrive at the PSD, when it is initially located on the dendrite, then the influx to the PSD is approximated by

$$J_{\text{inf}} = \frac{C_{\text{den}}}{\tau_{\text{D–S}}}. \tag{20}$$

According to the computations performed in Singer et al. (20), this flux depends on the geometric structures imposed by the spine and the PSD geometry. The value $\tau_{\text{D–S}}$ can be approximated by the expression

$$\tau_{\text{D–S}} = \frac{|\Omega_{\text{sH}}|}{2\pi D}\left(2\ln\frac{1}{\varepsilon} + \ln\frac{1}{\delta} + 3\log 2 - \frac{1}{2} + o(1)\right) + \frac{L^2}{2D}, \tag{21}$$

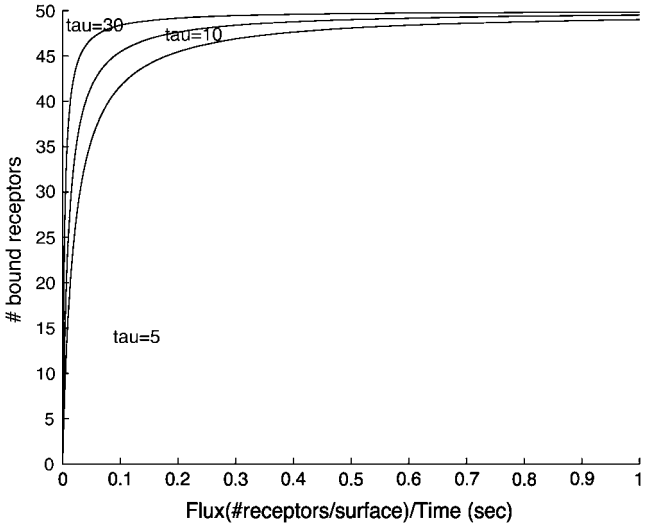

FIGURE 5 Modulation of bound receptors by the influx. For three different mean resident times, $\tau = 5$, 10, and 30 s, the number of bound receptors is given as a function of the influx. When the flux increases to 1/s, almost all PSD receptors are bound.

where $\Omega_{sH} = 4\pi R^2$ is the surface of the spine head (see (20)), ε is the ratio between the absorbing and the total arc length of the PSD boundary. The value δ is the ratio of the radius of the PSD to the radius of the spine head. The value L is the spine neck length. Equation 21 predicts in particular that τ_{D-S} depends quadratically on the spine length L. Equation 21 represents the sum of two mean times: the mean time a Brownian particle travels along the thin spine neck, but cannot return to the dendrite, plus the mean time it takes to enter into the PSD.

When the spine length L changes, because of the small spine neck radius, the flux converges to a new steady state. The arrival of receptors follows a Poisson process, therefore the relaxation to the steady state can be approximated by $J_{inf}^{-1}(1 - e^{-tJ_{inf}})$, which depends on the spine length. The time-dependent recovery is illustrated when the spine length increases from 0 to 0.2, 0.5, 1, and 2 μm in Fig. 4 (*top*). Another consequence of Eq. 21 is that a change in the radius of the spine head affects the mean time it takes for a receptor to enter the PSD. Changing the size δ of the PSD only modifies the time τ_{D-S} and thus the influx and the number of receptor at the PSD.

We conclude that dendritic spine geometry contributes to the regulation of the influx and thus of the number of receptors at the PSD. Another consequence of the spine shape is that the extrasynaptic membrane of the spine head can be interpreted as a buffer region because the spine neck separates the PSD from the dendritic shaft by a narrow area (see Fig. 4, *bottom*).

DISCUSSION

The main parameters we studied here are the number of scaffolding molecules, the influx of receptors in the PSD, and the geometry of the spine. Because all these parameters are not equivalent, we shall evaluate separately the role of each of them on the regulation of receptor dynamics.

From FRAP experiments to chemical constants of scaffolding molecule/receptor interactions in neurons

After FRAP experiments, unbleached receptors replenish the PSD by lateral diffusion and bind to the scaffolding molecules, as described by Eq. 18 with kinetics illustrated in Fig. 3. The time-course of unbleached receptors recovers exponentially and this curve can be used to fit experimental data. For example, it might be possible to estimate the backward binding constant when the other parameters such as the geometrical characteristics of the PSD, the forward binding rate, and the total number of scaffolding molecules are known.

In classical approaches, the mathematical theory used to analyze FRAP data has been developed in particular when the forward binding rate is large compared to other timescales such as diffusion. In that case, the recovery can be approximated by an exponential. When the values of the off- and on-rates are comparable, a system of differential equations (Eqs. 7 and 8) is used and, by fitting the data, an estimation of the rates and the number of binding sites can be obtained. When the diffusion timescale is dominant, models of free diffusion have been used associated with simple geometries, such as a square or a circle, while the effect of organelle barriers was studied in Olveczky and Verkman (21) using computer simulations. Finally, in the limit of a large number of molecules, when the diffusion and the binding processes have similar timescales, numerical results for a system of reaction-diffusion in free space have been obtained in Eqs. 7 and 8. Finally, a refined analysis was developed in Sbalzarini et al. (22) to estimate the consequence of the cell geometry on the effective diffusion constant. A theory of anomalous diffusion can be found in Saxton (24), while a computational method to analyze diffusion in curved surfaces is presented in Sbalzarini et al. (23). It should be stressed that compared to our approach, classical analysis did not account for the conjugated effects of the complex cell architectures, involving mixed boundaries (reflection and absorption) and small numbers of Brownian receptors.

Timescale of synaptic changes: scaffolding molecules versus influx modulation

By controlling calcium entry, neuronal activity modulates with a fast timescale the shape of the spines (23). This process is due to the phosphorylation and/or polymerization of molecules. By changing the cytoskeleton's local properties, the effective diffusion constant of receptors is modified due to reorganization of submembranous obstacles (1,2). Moreover, an increased activity induces an increase in the dendritic calcium concentration, which can then affect the geometry of all synapses simultaneously. Equation 17 indicates that a new steady state of scaffolding protein-receptor assembly is

achieved by modifying the receptor influx due to a reorganization of the spine geometry. Because neuronal activity can also control the number of scaffolding molecules (25–31), a new stable equilibrium of bound receptors can also be achieved. The regulation of scaffolding proteins is a fundamental process which contributes to the long-term stability of the synapse. Alternatively, changing the receptor fluxes is a transient, fast, and reversible process but cannot lead to a permanent change.

We conclude that two components are involved in synaptic dynamics regulation:

1. A global component, which can be induced by global neuronal activity, affecting all synapses and which can regulate calcium influx and thus spine geometry.
2. A local component regulating the number of scaffolding molecules. Possibly, by integrating the local depolarizations, a back-propagated action potential can be generated (31) which can ultimately modulate the number of scaffolding molecules.

The superimposition of components *1* and *2* may provide a mechanism by which the interaction of the local and global activity accounts for synaptic equilibrium and synaptic plasticity.

Synaptic receptor number can be regulated by spine motility

Dendritic spines are highly motile structures, which can change shape driven by neuronal activity (15,16,32–37). For example, high glutamate concentration produces a spine retraction, while a low concentration induces spine elongation (39). Since the length of the spine neck changes continuously (15), according to our analytical model, the influx of receptors at the PSD regulates the steady state of bound receptors: Eq. 21 indicates that spine length controls the number of receptors at the PSD. At steady state, the amplitude of the receptor flux and the number of scaffolding molecules determine the number of bound receptors. When the spine length increases, the receptor influx diminishes, as does the number of bound receptors.

In relation to glutamatergic transmission, a high level of transmitter release will shorten the spine length, and will subsequently increase receptor influx to the spine head. This mechanism provides a substrate for the regulation of receptor diffusion. Spine length is already known to control the degree of the spine-dendrite calcium communication (15). We propose now that spine geometry can also control, by lateral diffusion, the number of receptors at the PSD at steady state and thus the synaptic strength.

Homeostasis and lateral diffusion of receptors

Homeostasis is a compensatory mechanism at synapses, by which the synaptic response is scaled (18,40) so that the balance of excitatory and inhibitory transmission is maintained. Blocking spontaneous activity in cultured neurons for long periods of time results in a compensatory scaling (41). In addition, acutely reducing inhibition in cortical neurons results also in hyperactivity, which will ultimately reduce the activity (41). The scaling effect is correlated with a change in the mEPSC amplitude, indicating that this form of adaptation results in a global change of synaptic weight at synapses, while preserving their relative weights. We propose here to link neuronal activity with receptor trafficking in and out of synapses.

At steady state, it has been shown analytically that the postsynaptic calcium concentration is proportional to the mean frequency of presynaptic action potentials (5). Calcium concentration controls actin polymerization and/or protein phosphorylation. Recent experiments (S. Lévi, Ecole Normale Superieure, personal communication, 2006) show that actin depolymerization results in an increase in the apparent diffusion constant of receptors. These results suggest that increasing calcium concentration induces actin polymerization which reduces and confines the receptor movement. Moreover, calcium could control indirectly the number of scaffolding proteins, since changes in activity have been shown to modify not only the number of receptors but also the level of scaffolding proteins (41). Using these experimental results, we conclude that the influx J_{in} is a decreasing function of calcium concentration, which is itself a linear function of the mean firing rate f. Using the present model, a possible scenario for the initial phase of homeostasis scaling is as follows: when the mean activity f increases, the mean calcium increases and thus the influx J_{in} diminishes. According to Eq. 17, the number of bound receptors at the PSD decreases. We conclude that the synaptic weight is decreased. When the mean activity decreases, the system scales in the opposite direction.

To achieve a stable regime, the homeostatic regulation should also involve a change in the number of scaffolding molecules. It is also possible that the chemical apparent reaction constants k_2, k_{-2} depend on the mean synaptic calcium concentration.

Based on experimental data, it has also been reported that neuronal activity regulates the ER export and/or recycling of receptors toward the plasma membrane (27,41,42). When intracellular receptors are inserted directly at the PSD, the inward flux is the sum of two fluxes $J_{\text{in}} = J_{\text{extra}} + J_{\text{intra}}$, where J_{extra} is the extrasynaptic flux (lateral diffusion) and J_{intra} is the intracytoplasmic flux (insertion at synapses). Ultimately, receptor fluxes at synapses can be modulated by changing the position of the endocytosis sinks or exocytosis sites, which affect the local concentration of extrasynaptic receptors. Finally, one can postulate that the total number of scaffolding molecule-receptor can be divided into two groups:

1. The first group is the set of scaffolding molecules S_{endo} bound to receptors, which cannot move by lateral diffusion.

2. The second group is the set of scaffolding molecules S_{extra}, which can bind dynamically to extrasynaptic receptors.

The first group would ensure a certain stability of the synapses on a timescale of days, while the second group would be used to modulate synaptic responses on a shorter timescale.

Pre- and postsynaptic determinants of variability

The overall probability that the presynaptic neuron releases neurotransmitters is ~20% with a large variance (43). Another source of fluctuations also exists at the postsynaptic site. These fluctuations are due to the receptor fluxes modulating the synaptic weight, as we have shown by Eq. 12 (see also Fig. 2 *b* for the *variance curve*). An additional source of fluctuation arises from the possibility that postsynaptic receptor properties may be changed when receptors are bound to scaffolding molecules. Such is the case for AMPA receptors bound to stargazin and PSD95, which have a higher opening rate, resulting in a slower desensitization and deactivation (14).

The regulation of lateral diffusion and transient capture by scaffolding proteins may act on key parameters such as τ_1 (the mean exit time) and $\vartheta \gg 1$ (an equilibrium parameter in Eq. 9). If the fluxes of receptors are large (i.e., $\vartheta \gg 1$), the PSD will be saturated with a large number of free receptors. Then the equilibrium of bound receptors will be achieved. In that case, the presynaptic element is the main source of fluctuations. However, if the fluxes of receptors are small, the variance of receptors bound to scaffolds will be large and then the PSD also contributes to fluctuations in synaptic efficacy.

If fluctuations are inherent to the system, one possible way to overcome uncertainty and gain reliability is to couple, by afferent axons, multiple presynaptic units with identical postsynaptic ones.

CONCLUSION

In a simplified model, we have proposed a generic system of equations that account for the dynamics of receptors at the PSD. Our model generalizes previous models used to interpret FRAP experiments, and can be used to extract the value of parameters useful for a detailed description of the physiology of synapses. Receptor dynamics are characterized not only by the time needed to enter/leave the PSD but also by the time required to bind to and dissociate from the scaffolding molecules. Because neuronal activity can change the composition of the synapse, future models should be adapted to various types of receptors, such as AMPA, NMDA, GABA, and the glycine receptor.

APPENDIX: DERIVATION OF THE GENERAL EQUATIONS

We provide in the Appendix the exact expression of the mean and the variance of bound receptors at the PSD. We derive a master equation for the joint probability $p_{k,q}(t) = Pr\{N(t) = k, Q(t) = q\}$ of having k bound receptors and a total number of receptors $Q(t) = q$ at time t. We obtain the following expressions for the mean and the variance:

$$M(t) = \sum_{k=1,..S_0} \sum_{q \geq k} k p_{k,q}(t), \tag{22}$$

$$\sigma^2(t) = \sum_{k=1,..S_0} \sum_{q \geq k} k^2 p_{k,q}(t) - M^2(t). \tag{23}$$

To derive the master equation, we estimate the variation in the number of bound receptors during times t and $t + \Delta t$. As discussed in Results, there are two causes of fluctuations. The first is due to the exchange of receptors with the rest of the dendrite, that is $q \to q - 1$ or $q \to q + 1$, and the second due to receptor binding $k \to k + 1$ and $k \to k - 1$, dissociating from scaffolding molecules. We obtain for $k = 1..S_0$ and $q \geq k$ (44), that

$$\begin{aligned}\dot{p}_{k,q} = &-\left[k_{-2}k + k_2(q-k)(S_0-k) + \langle J_{in}\rangle + \frac{q-k}{\tau_1}\right]p_{k,q} \\ &+ k_{-2}(k+1)p_{k+1,q}(t) + k_2(q-k+1)(S_0-k+1)p_{k-1,q} \\ &+ \langle J_{in}\rangle p_{k,q-1} + \frac{q+1-k}{\tau_1}p_{k,q+1}\end{aligned}$$

and $q \geq 1$,

$$\begin{aligned}\dot{p}_{S_0,q} = &-\left[k_{-2}S_0 + k_2(q-S_0+1) + \langle J_{in}\rangle + \frac{q-S_0}{\tau_1}\right]p_{S_0,q} \\ &+ k_2(q-S_0+1)p_{S_0-1,q} + \langle J_{in}\rangle p_{S_0,q-1} + \frac{q+1-S_0}{\tau_1}p_{S_0,q+1},\end{aligned}$$

$$\begin{aligned}\dot{p}_{0,q} = &-\left(k_2 q S_0 + \langle J_{in}\rangle + \frac{q}{\tau_1}\right)p_{0,q} + k_{-2}\,p_{1,q} + \langle J_{in}\rangle p_{0,q-1} \\ &+ \frac{q+1}{\tau_1}p_{k,q+1},\end{aligned}$$

and

$$\dot{p}_{0,0} = -\langle J_{in}\rangle p_{0,0} + \frac{1}{\tau_1}\dot{p}_{0,1}.$$

When the binding time constant is much smaller than the trafficking time constants, that is $k_{-2} \ll k_2$, τ_1, we recover the approximation that $p_{k,q}(t) \sim p_k(t|q)Q_q(t)$, where Q is given by Eq. 3. This Markov chain can also be used to fit FRAP experiments when the number of bleached receptors is small.

Brief derivation of Eqs. 7 and 8

Equation 7 is solved directly by induction. First one has to express (see also (45)) Q_1 as a function of Q_0 using the first relation in Eq. 3 and then Q_2 as a function of the Q_0, Q_1 using the second relation in Eq. 3. All terms of the sequence can then be expressed as a function of Q_0. Finally, to determine the value of Q_0, it is necessary to use the normalization condition, which says that the sum of the probability that the number of receptors inside the PSD is equal to k is exactly 1: $\sum_{k=0}^{\infty} Q_k = 1$. We obtain the standard Poisson distribution.

Equation 8 is solved similarly by induction, but the number of bound scaffolding molecules can only be a number between 0 and S_0.

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