Estimating the synaptic current in a multi-conductance AMPA receptor model

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Abstract

A pre-synaptic neuron releases diffusing neurotransmitters such as glutamate that activate post-synaptic receptors. The amplitude of the post-synaptic current, mostly mediated by glutamatergic (AMPARs) receptors, is a fundamental signal that may generate an action potential. However, although various simulation results [10, 13, 14] have addressed how synapses control the post-synaptic current, it is still unclear how this current depends analytically on factors such as the synaptic cleft geometry, the distribution, the number and the multi-conductance state of receptors, the geometry of post-synaptic density (PSD) and the neurotransmitter release location. To estimate the synaptic current maximal amplitude, we present a semi-analytical model of glutamate diffusing in the synaptic cleft. We modeled receptors as multi-conductance channels and we find that PSD morphological changes can significantly modulate the synaptic current, which is maximally reliable (the coefficient of variation is minimal) for an optimal size of the PSD, that depends on the vesicular release active zone. The existence of an optimal PSD size is related to nonlinear phenomena such as the multi-binding cooperativity of the neurotransmitter to the receptors. We conclude that changes in the PSD geometry can sustain a form of synaptic plasticity, independent of a change in the number of receptors.
Introduction

Synapses are local active micro-contacts underlying direct neuronal communication. Depending on the brain area and the neuron types, synapses can vary in size and molecular composition. These inter-synaptic variations are mediated by hundreds of different molecules and proteins, participating in the assembly of the stable but plastic synaptic structure (1–4). Neurotransmitters such as glutamate molecules, after being released from vesicles, diffuse in the synaptic cleft, between the pre and post synaptic terminals (Fig.1). The post-synaptic terminal of excitatory synapses contains ionotropic receptors such as AMPA and NMDA receptors and they may open upon binding with neurotransmitters. AMPARs are tetrameric assemblies composed of four different subunits, which can bind to a glutamate molecule (5), but it has been reported that two agonist molecules at least are required to open a single AMPA channel (6). The amplitude of ionic current is thus proportional to the number of open receptors and their conductances. The postsynaptic current measures the efficiency of synaptic transmission and reports in a complex manner the frequency and location of released vesicles (2).

It is intriguing that although the number of neurotransmitters released is of the order of thousands, the number receptors is at most one hundred. This difference may serve to compensate the small receptor patches that should be found by the neurotransmitters (37). To study synaptic transmission, a fundamental step was the analysis of channels such as AMPARs, expressed in oocytes. By recording the current using patch clamp and excised patch, the conductance state properties, related to the open, closed and desensitized states have been extracted by Markov chain models (6–8). However, to reduce the complexity of AMPARs dynamics, Markov chains were kept as minimal as possible, based on one or two possible binding sites (6–8) with a single conductivity level. Only recently (10), to study the high variability ($\sim 5 - 100$ pA) of the synaptic current $I_s$, a four state channel model was used to interpret the high coefficient of variation, which was shown to be due to the spatiotemporal correlations of two released vesicles. When the receptor properties have been sufficiently well characterized, a second step consisted in integrating these properties within the synaptic organization to reconstruct the synaptic function. This step became possible by the use of modeling and numerical simulations (10, 12, 14, 16) allowing to estimate the role of synaptic geometry on the number of open receptors. More recently using glutamate diffusion and electrical resistance properties of the synaptic cleft, it was anticipated that the synaptic current could be maximal for an
optimal cleft height \[ h_{optimal} \].

We find here by deriving a novel semi-analytical approach that the synaptic current depends on the vesicular release location, the number and the biophysical properties of the receptors, the PSD size and location, and the geometrical characteristics of the synaptic cleft. To obtain these estimates, we model glutamate as diffusing molecules and approximate the cleft geometry as a narrow cylinder \[ (21) \]. But instead of using the classical Markov description \[ (6–8) \], our analysis relies on some direct analysis of AMPA conductances states \[ (5) \] and we account for the four glutamate binding sites per receptor. Our analysis reveals that given the pre-synaptic active zone size, where vesicles are released, the coefficient of variation (CV which is the standard deviation divided by the mean) of the synaptic current is minimal for a specific PSD size and all other sizes, that may be induced by plastic changes\[ (23) \], lead to an increasing CV. However, for a centered active zone, we show that for a fixed density of receptors, the synaptic current is always a decreasing function (to zero) of the PSD radius. We further show that a maximal and reliable current cannot be achieved simultaneously for the same distribution of synaptic parameters. Finally, we will propose that a synapse can increase its reliability by restricting the active zone (AZ) radius, which is a unique and nonlinear function of the PSD radius. This result should be true for generalized geometry and not only geodesic disks. Finally, remodeling the PSD, which affects the synaptic current, can occur in parallel with the classical synaptic modulation, induced by the direct addition or removal of synaptic receptors. PSD remodeling can be mediated by geometrical or internal scaffolding reorganization \[ (22, 23) \], that can be transient but much faster than changing permanently the synaptic receptors. These fast changes can thus affect the detection threshold of the post-synaptic neuron \[ (22, 24, 25) \] and be a source of synaptic plasticity without changing the number of AMPARs.

**Method: Theoretical model**

**Diffusion in the synaptic cleft.**

The synaptic current \[ I_s \] is mediated by open AMPARs, which can bind from one to four glutamate molecules. A single AMPAR has several conductance states which correspond to the combination of the four distinct conductances, associated to the different GluR subunits \[ (5, 26) \]. However, to reduce the complexity of the analysis, most studies \[ (6, 8, 11, 14, 15) \] have modeled AMPARs dynamics by one or two bound glutamate molecules. The
conductances designated by $\gamma_1, \gamma_2, \gamma_3, \gamma_4$ associated with 1, 2, 3 or 4 bound glutamate molecules. It has been reported (27, 28) that at least two glutamate molecules are needed to open an AMPAR, so we set $\gamma_1 = 0$. The synaptic current $I_s(t)$ depends on the number of open channels ($N_2, N_3, N_4$) bound respectively by 2, 3 or 4 glutamate molecules. In that case,

$$I_s(t) = (\gamma_2 N_2(t) + \gamma_3 N_3(t) + \gamma_4 N_4(t))\Delta V, \quad (1)$$

where $\Delta V$ is the difference of potential between the intra and the extracellular medium. We selected from the experimental results (5), obtained for different glutamate concentration the values $\gamma_2 = 4 pS, \gamma_3 = 10 pS, \gamma_4 = 13 pS$ (for $\Delta V_m = -100 mV$).

Our goal here is to estimate the mean and the variance of open receptors and quantify the peak amplitude of the current $I_s$. After a vesicle fuses with the pre-synaptic membrane at position $x_0$, $N_g = 3000$ glutamates are released (Fig.1). Glutamate molecules diffuse in the cleft and are reflected on the synaptic membrane, while they are absorbed at the lateral boundary of the synaptic cleft. AMPARs are uniformly distributed over the PSD. We consider that only a certain fraction of glutamates hitting an AMPAR leads to receptor activation, due to a chemical energy barrier. The synaptic cleft is modeled as a cylinder $\Omega$ (Fig.1), while there are $N_a$ AMPARs located on the PSD. When a glutamate molecule hits an AMPAR, it can either be reflected or it will activated the receptor. We model this behavior using a homogenized radiative boundary condition over the entire PSD ($\partial\Omega_{PSD}$) (30–32). A glutamate that hits the neuron membrane is reflected except at the lateral cleft boundary ($\partial\Omega_{Lat}$), where it will not contribute to activate an AMPAR and this is modeled by an absorbing boundary condition.

**Estimating the number of open receptors.**

The probability to find a glutamate molecule at position $x$ at time $t$, when it started at position $x_0$ is given by the density function $p(x,t|x_0)$ that satisfies the equation:

$$\frac{\partial p(x, t| x_0)}{\partial t} = D \Delta p(x, t| x_0), \quad x \in \Omega, \ t > 0 \quad (2)$$

$$\frac{\partial p(x, t| x_0)}{\partial \nu} \bigg|_{\partial \Omega_r} = 0, \quad p(x, t| x_0) \bigg|_{\partial \Omega_{Lat}} = 0$$

$$-D \frac{\partial p(x, t| x_0)}{\partial \nu} \bigg|_{\partial \Omega_{PSD}} = -\kappa p(x, t| x_0),$$
where $D$ is the free glutamate diffusion constant. The partial absorption constant $\kappa$ accounts for the fraction of AMPARs inside the PSD and the activation barrier of a glutamate to a GluR binding site. Using a homogenization procedure (30–32, 40), we shall derive a new expression in the context of the synaptic cleft for the partial reflection parameter $\kappa$

$$\kappa = \frac{D}{2\pi R_{PSD}^2 f(\sigma) + \frac{D}{\kappa_a N_a}}$$  \hspace{1cm} (3)

where $f(\sigma) = 1 - \sigma$, $\sigma = N_a a^2 / R_{PSD}^2$, $a$ is the radius of the binding site and $R_{PSD}$ is the radius of the PSD and $\kappa_a$ measures the partial binding of a glutamate molecule to a single receptor. We have summarize in the appendix all these steps. To determine the constant $\kappa_a$, we used the fitted results obtained from the Markov analysis given in (7). In a first approximation neglecting $\kappa_a$, the partial reflecting constant $\kappa$ is directly proportional to the binding rate of glutamate molecules and in the appendix, we obtain the numerical approximation $\kappa_a \approx 1.06$.

To determine the value of $\kappa$ (see appendix 1.2) we further need to estimate the effective radius $a$ of a single receptor. For that purpose, we run some simulations for a typical synapse of radius 500nm with a PSD radius of 300nm, a height of 30nm and an AZ radius of 150nm. Using the criteria that the synaptic current saturates for four released vesicles ($\sim 12,000$ glutamate molecules), we obtain that radius $a \approx 1.8nm$, as shown in figure (3). Interestingly, the radius $a$ accounts not only for the geometrical properties of the AMPAR binding site, but also for the underlying electrostatic interactions. This value $a$ should be compared to the recent crystal structure dimensions (the AMPAR has a transversal size of 9nm and the total length is around 18nm) of the ligand-binding domain reported to be less than 4nm (33).

The probability $p(x_0)$ that a glutamate molecule released at position $x_0$, binds a receptor is given by the total flux:

$$p(x_0) = -D \int_0^\infty \int_{\partial \Omega_{PSD}} \frac{\partial p(y,t|x_0)}{\partial n} dy dt = -D \int_{\partial \Omega_{PSD}} \frac{\partial u(y|x_0)}{\partial n} dy$$
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where $u(x|x_0) = \int_0^\infty p(x,t|x_0)dt$ satisfies

$$D \Delta u(x|x_0) = -\delta(x-x_0) \quad \text{for} \quad x \in \Omega$$

$$\frac{\partial u(x|x_0)}{\partial \nu} |_{\partial \Omega_{\text{r}}} = 0, \quad u(x|x_0)|_{\partial \Omega_{\text{Lat}}} = 0$$

$$D \frac{\partial u(x|x_0)}{\partial \nu} |_{\partial \Omega_{\text{PSD}}} = -\kappa u(x|x_0),$$

In the appendix, we derive an analytical expressions of $u$ and $p$. For a vesicle releasing its contain at the center of the AZ, the probability to bind one of the AMPARs is

$$p = \frac{J_{\text{PSD}}}{J_{\text{PSD}} + J_{\text{Lat}}},$$

where

$$J_{\text{PSD}} = 2\pi \kappa \int_0^L \frac{1}{D} K_0(\alpha r)rdr + 2\pi \kappa \int_0^L AI_0(\alpha r)rdr$$

and

$$J_{\text{Lat}} = -2\pi DhC.$$
where \( N_g \) is the total number of released glutamate molecules. Because AMPARs can bind from zero to four glutamate molecules, the probability of a given configuration \( \vec{n} = (n_4, n_3, n_2, n_1) \) to have \( n_1 \) AMPARs bound to one glutamate, \( n_2 \) AMPARs bound to two glutamates and so on, when there are \( N_a \) AMPA receptors, for \( k \leq \min(4N_a, N_g) \) bound glutamate molecules, is given by

\[
\Pr\{\vec{n}|k\} = \frac{N_a!}{n_4!n_3!n_2!n_1! (N_a - (n_4 + n_3 + n_2 + n_1))!} F(k, N_a),
\]

where this probability is computed by choosing \( n_4 \) AMPARs out of \( N_a \), \( n_3 \) out of \( N_a - n_4 \) and so on. \( F(k, N_a) \) is the number of possibilities to decompose the integer \( k \) on the integer \( 4, 3, 2, 1, 0 \), when there are at most \( N_a \) terms: that is \( k = 4n_4 + 3n_3 + 2n_2 + n_1 \). In practice, we compute \( F(k, N_a) \) numerically as the \( k+1 \)'s coefficient of the expression \((1 + x + x^2 + x^3 + x^4)^{N_a}\). The present analysis can be used to obtain any statistical moments associated to the current and in particular, the mean and variance

\[
\langle I_s(x_0) \rangle = \Delta V \sum_{k=1}^{N_a} \sum_{n \in S_k} (\vec{n} \cdot \vec{\gamma}) Pr\{\vec{n}|k\} Pr_k(x_0) = \Delta V \sum_{k=1}^{4N_a} \sum_{n \in S_k} (\vec{n} \cdot \vec{\gamma}) Pr\{\vec{n}|k\} Pr_k(x_0) + \Delta V N_a \gamma_4 \left(1 - \sum_{k=0}^{4N_a} Pr_k(x_0) \right)
\]

\[
\langle I_s^2(x_0) \rangle = \Delta V^2 \sum_{k=1}^{N_a} \sum_{n \in S_k} (\vec{n} \cdot \vec{\gamma})^2 Pr\{\vec{n}|k\} Pr_k(x_0) - \langle I_s(x_0) \rangle^2 = \sum_{k=1}^{N_a} \sum_{n \in S_k} (\vec{n} \cdot \vec{\gamma} \Delta V)^2 Pr\{\vec{n}|k\} Pr_k(x_0) + (N_a \gamma_4 \Delta V)^2 \left(1 - \sum_{k=0}^{4N_a} Pr_k(x_0) \right) - \langle I_s(x_0) \rangle^2
\]

where \( \Delta V \) is the voltage drop, \( \vec{\gamma} = (\gamma_1, \gamma_2, \gamma_3, \gamma_4) \) is the conductances vector, \( S_k \) represents the set of possible configurations of \( \vec{n} = (n_1, n_2, n_3, n_4) \) such that \( 4n_4 + 3n_3 + 2n_2 + n_1 = k \). The formulas for the mean and variance are made of two terms: the first is the sum over all the sites that are partially
bound by glutamate molecules and the probability for such an event is the product of the probability $P r_k$ that $k$ glutamates are bound ($k < 4N_a$) and the probability $Pr\{\vec{n}|k\}$ of a given binding configuration $k = 4n_4 + 3n_3 + 2n_2 + n_1$. The second term accounts for all bound AMPARs ($4N_a$) and this happens with the complementary probability to the first case.

**Numerical simulation results for the synaptic current**

To determine the maximum amplitude of the synaptic current, we use our semi-analytical method developed above and simulate a single vesicle ($N_g = 3000$) released. We find (Fig.2A) that AMPARs are mostly bound to two glutamate molecules, while for already two vesicles, the dominant contribution comes from receptors bound to four. To further investigate the influence of the PSD size on the synaptic current, we plotted the current $I_s$ as a function of the release site position (Fig.2B): when release occurs outside the region above the PSD, the current drops drastically due to a fast decay of the binding probability.

Since our analysis allows us to determine the relative influence of the AZ and the PSD, we vary their respective sizes and we estimate the consequences on the synaptic current. We first plotted in figure 4A, the mean and variance of $I_s$ as a function of the PSD radius when one vesicle is released at the center. We find that for a given density of receptors, the current is a decreasing function of the PSD radius. In figure 4B-C, we plotted the number of AMPARs bound to two, three and four glutamate molecules when we fix the AZ radius to 50nm (blue) and 150nm (red). For a small AZ radius, the AMPARs are in majority bound to four glutamate molecules and thus the synaptic current amplitude is much higher compared to the case of a large AZ radius. In that latter case, the current is primarily generated by receptors bound to two glutamate molecules. We can now use our refined analysis to re-interpret the large current differences observed in figure 4A with the radii 50nm and 150nm. This difference is due to the nonlinear properties of having different conductivities, generated by the amount of bound glutamate molecules. But in all cases, the synaptic current is a decreasing function of AZ radius (Fig. 4D).

To assess the reliability of the synaptic response, we use the coefficient of variation (CV=standard deviation over the mean) of the synaptic $I_s$. For a fixed AZ radius, we now show that the CV has a minimum as function of the PSD radius: Indeed, using our simulation results 4E, we find for example
with an AZ of radius 100 nm, that the CV reaches its minimum for a PSD radius of 120 nm. In order to confirm this result, we performed Brownian simulations associated with our semi-analytical model. This Brownian simulation is described as followed: glutamate molecules are released from the AZ of radius 250 nm and diffuse in a synapse of radius 500 nm. We run simulations (fig.6A) for various PSD sizes and computed the associated CV (for an average of 100 samples). In the simulations, a receptor is modeled as a partial absorber and when it binds to four glutamate molecules, it becomes totally reflecting. The current is computed using equation 1. Finally, any glutamate molecule reaching the lateral boundary of the synapse is permanently absorbed. Using these rules, We find (fig.6B) that our initial analysis is confirmed by the Brownian simulations.

To further investigate the relation between the radius of the PSD and the AZ, we plotted (figure 4F) the optimal PSD radius as a function of the AZ size. We find that the optimal PSD size increases with the size of the AZ, but the relationship is a nontrivial nonlinear. To see whether the size of a synapse affects the CV curve, we fixed the AZ radius at 50 nm and plotted the synaptic current as a function of the PSD radius for four different synapses of sizes 200, 300, 400, and 500 nm (Fig.5). Interestingly, as shown in Fig.5B, the value of the PSD for which the optimal CV is achieved, does not depend much on the synaptic radius. We observe that the CV is a decreasing function of the synaptic radius and thus large synapses are more reliable than small ones. Finally, to assess the role of a possible fluctuation in the number of glutamate molecules released from a vesicle, we show in figure Fig.5C the effect of three different distributions for 2000, 3000, and 4000. This shows very little change in the CV minimum phenomena. In Fig.5D, we compare release where the mean number is 3000 molecules with a variance of 500 Gaussian distributed (bold line) with a release of a fixed number 3000 (dashed line). We observe a small deviation, showing that in this range of fluctuation, the number of released glutamate molecules does not affect much the CV.

Discussion

We have analyzed here the synaptic current $I_s$ starting from the intrinsic biophysical properties of the AMPARs (5). We included the diffusion of glutamate molecules in the narrow synaptic cleft and estimated the fraction that binds AMPARs. Contrary to previous works (6, 11, 14, 15), our analysis does not use the description of channels involving a time dependent multi-
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states Markov chain, instead we use a multi-conductance approach mixed with a time independent receptor description. In addition, we neglected any possible interactions between bound receptor subunits that would affect the probability for a free subunit to bind a glutamate molecule. This approach allows us to obtain semi-analytical results about the synaptic current and to account for the nonlinear effect due to the multi-conductance states of bound AMPARs. We also studied the role of the cleft geometry and explore the role of several parameters.

For example, we have found here that modulating the PSD size can affect the synaptic current amplitude: the current depends on the relative size of the PSD to the AZ (Fig. 4A,D). As a consequence, because the PSD could be reorganized, while the total number of receptors remains constant, we propose that this direct change in the PSD geometry can modulate the synaptic current. These functional consequences were anticipated in recent experiments using GFP-tagged PSD-95 (23). As suggested there, the PSD size is in constant remodeling. Thus, combined with our analysis, we propose that synaptic changes are a source of synaptic current modulation. It is not clear what are the reasons for these changes, but they could be induced by long term potentiation (LTP) or depression protocols (23). Changing PSD size, while keeping AZ fixed can be seen as a form of plasticity induced by structural remodeling without any change in the number of receptors. These changes can, for example, be induced by actin dynamics, which is correlated with spine shape changes (34, 35).

We have not accounted here neither for glial cells nor neuronal transporters, that only weakly affect direct synaptic transmission and the number of open AMPARs. The effect is of the order 10% − 15% ((14),(16) Figure 9, (18), (17),(19)). However, in some pathological conditions, related to a glial reorganization, glial transporters can directly modulate synaptic transmission (9), which changes drastically the present results.

Another aspect of our modeling approach relies on the description of AMPARs. Indeed, we computed the synaptic current from conductances originating from patch-clamp experiments of isolated AMPARs (5, 29), where the relation between the number of bound glutamates and the associated conductances was obtained for different fixed glutamate concentrations. Although more than four conductance levels have been reported, it is still unclear how to relate them to the number of bound glutamate molecules. In that context, it would be interesting to design a specific experiment to measure simultaneously on single AMPAR the number of bound glutamate and the associated current. In addition, having four glutamate bound to a single receptor lead to an amplitude of 13 pA, which has to be compared...
with two bound AMPARs to two glutamates leading to \( 2 \cdot 4 = 8 \) pA). This
difference suggests that binding four glutamates to a single AMPAR has a
nonlinear effect and is different from having two receptors bound by two glu-
tamates, as reported in figures 4A-4B and 4C. To show that the minimum
of the CV comes from this nonlinearity, we shall now consider a reduced
model for single receptor with three states, immersed in an ensemble of \( N \)
binding molecules. Depending on the number of bounds, the receptor can
be in one of the three states, where the current \( I \) can switch between the
three values \( I_1, I_2, I_3 \). Each molecule binds with a probability \( q \in [0, 1] \)
and the probability of \( I \) is given by

\[
p(I = I_k) = \begin{cases} \binom{N}{k} q^k (1 - q)^{N-k} & k = 1, 2 \\ 1 - p(I = I_1) - p(I = I_2) - (1 - q)^N & k = 3. \end{cases}
\]

where the probability for one and two is given by the Binomial law while to
compute the probability for the current \( I_3 \), we use that it is the difference
of the first twos minus the probability that no molecules are bound. We
computed analytically the CV of the current \( I \) as a function of the probabil-
ity \( q \) and we observed (Fig. 6B) that only for some range of the parameters
such as \( I_1, I_2 \ll I_3 \), the CV presented a local minimum. This results show
this simple model captures the features for a minimum. In addition, in that
model changing the parameter \( q \) is equivalent to vary AZ or the PSD radius.

To conclude, it is still unclear what defines the detection threshold of
a post-synaptic neuron. Indeed, this current is mediated by the number
of open AMPARs and the associated conductances. When an AMPAR is
maintained at the PSD by scaffolding molecules such as PSD-95, located
just underneath the location of vesicular released (a signal that can be medi-
ated by N-cadherin molecules (22)), the probability of glutamate binding is
maximal and thus the AMPARs will report more accurately this vesicular
event. We predict that this effect will be increased when the scaffolding
molecules PSD-95 will be over-expressed. Indeed the over-expression will
results in an increasing of the number of anchored receptors and their rel-
ative location in comparison with the pre-synaptic terminal. In contrast,
in PSD-95 knockdown (by shRNA (25)), the detection threshold was found
to be lower, due to a decrease in the number of AMPARs and a dispersive
AMPAR configuration.

A synapse is an unreliable device but the variability is reduced when
the AZ and the PSD are apposed with a precise relationship between their
radius (Fig. 4F). However, if the vesicular release is spread over the AZ,
receptors over the PSD can detect a vesicular event, but it might be very small. The regulation of the PSD size should thus be a fundamental parameter comparable to increasing the AMPAR number, which is the molecular basis for robust synaptic plasticity. Finally, from a biophysical point of view, the partial reflection constant that have introduced for the simulation of the AMPARs reflects both the energy activation barrier of glutamate-AMPAR interaction and the probability to find a receptor inside the PSD. The concept of alignment of vesicular release domain with the PSD was already suggested in (36) without quantitative analysis. Thus changing the PSD shape can modulate the synaptic current and thus can be considered as a source of plasticity. It would be interesting to analyze the molecular mechanisms responsible for such changes (23).

1 Appendix

Summary of our methodology approach

We shall now summarize our methodology and the organization of this appendix. Our new method consists in combining analytical computations and numerical simulations to estimate the probability that a combination of glutamate molecules activate an AMPAR, with direct experimental measured conductances (5). The methodology to estimate the distribution of bound AMPARs is first to compute the probability that glutamate molecule binds a receptor. For this we solve in appendix 1.1 the probability equation and calculate the flux of receptors to a given region (the PSD) and the total flux through all the synaptic cleft as a function of variable \(x\), position where glutamate molecules are released. The ratio of the fluxes is the probability. Second, because the height of the synaptic cleft is small, the solution \(u\) of equation (9) is close to its average over the z-direction and we use this property to perform our computations. Third, we consider that the AMPARs are uniformly distributed over the PSD and we use a homogenization procedure to replace by a partial reflecting boundary condition summarized in the constant \(\kappa\), a complicated boundary condition, where sometimes a glutamate molecule would bind to an AMPAR receptor with a given probability of activation and sometimes it would be reflected when hitting parts of the PSD containing no receptors. Fourth, the rational expression for \(\kappa\) is derived in appendix 1.2 and the associated mathematical derivation is given in appendix 1.5. To check the validity of our computation, we compare our results with Brownian simulation, described in appendix 1.3. Finally, we use published data to obtain an approximate value for \(\kappa\) and relate it to the
activation and the effective binding size of a single AMPAR (appendix 1.4).

1.1 Analytical expression for the binding probability of a glutamate molecule to the PSD, using an averaging method.

We present here an averaging method to obtain an explicit expression for the probability $p(x_0)$ that a glutamate binds one of the AMPA receptors before it escapes. To compute the total number of bound glutamate molecules to the AMPARs, we solve the steady state diffusion equation in the cylindrical synaptic cleft geometry, where glutamate is released at $x_0$. Using an averaging method, we analyze equation

$$D \Delta u(r, z) = -\delta(r)\delta(z - z_0) \text{ for } \{(r, z)|r \in [0, R), z \in (0, h)\} \quad (9)$$

$$\left. \frac{\partial u(r, z)}{\partial r} \right|_{\partial \Omega_{PSD}} = 0, \quad u(r, z)|_{r=R} = 0$$

$$D \left. \frac{\partial u(r, z)}{\partial r} \right|_{r<L, z=0} = -\kappa u(r, z),$$

In cylindrical coordinates, the average $\bar{u}(r) = \frac{1}{h} \int_0^h u(r, z) dz$ satisfies

$$D \left( \bar{u}''(r) + \frac{1}{r} \bar{u}'(r) - \frac{1}{h} \frac{\partial}{\partial z} u(r, 0) \chi_{[0,L]}(r) \right) = -\frac{1}{rh} \delta(r), \quad (10)$$

Using the boundary conditions on $\partial \Omega_{PSD}$ for $r < L, z = 0$, we express $\frac{\partial}{\partial z} u(r, 0) \chi_{[0,L]}(r) = 0$ in terms of $\bar{u}$:

$$u(r, z) \approx u(r, 0) + \frac{\partial u(r, 0)}{\partial z} z + O(h^2).$$

Integrating the Taylor expansion with respect to $z$, and using that for $u(r, 0) = \frac{D}{\kappa} \frac{\partial u(r, 0)}{\partial z}$ and $r < L$,

$$\bar{u} \approx \frac{\partial u(r, 0)}{\partial z} \left( \frac{D}{\kappa} + \frac{h}{2} \right), \quad (11)$$

by substituting eq. (11) in (10), we get

$$D \left( \bar{u}''(r) + \frac{1}{r} \bar{u}'(r) - \frac{2\kappa}{h(2D + \kappa h)} \bar{u} \chi_{[0,L]}(r) \right) = -\frac{1}{rh} \delta(r).$$
The solution is given by

\[ \bar{u}(r) = \begin{cases} \frac{1}{2\pi D} K_0(\alpha r) + AI_0(\alpha r) & 0 < r < L \\ C \log \frac{r}{R} & L < r < R \end{cases}, \]

where

\[ \alpha = \sqrt{\frac{2\kappa}{h(2D + \kappa h)}}. \]

To determine the parameters \(A\) and \(C\), we use the continuity of \(\bar{u}\) and its derivative at \(r = 0\). We obtain the linear system to invert:

\[ \begin{align*}
\frac{1}{D} K_0(\alpha L) + AI_0(\alpha L) &= C \log \frac{L}{R} \\
\frac{-1}{D} \alpha K_1(\alpha L) + A\alpha I_1(\alpha L) &= C \frac{1}{L}.
\end{align*} \]

The solution to these equations is given by

\[ \begin{pmatrix} A \\ C \end{pmatrix} = \begin{pmatrix} \alpha I_0(\alpha L) & -\log \frac{L}{R} \\ \alpha I_1(\alpha L) & \frac{1}{L} \end{pmatrix}^{-1} \begin{pmatrix} -\frac{1}{D} K_0(\alpha L) \\ \frac{-1}{D} \alpha K_1(\alpha L) \end{pmatrix} = \frac{1}{D\alpha (\log \frac{L}{R} I_1(\alpha L) - L^{-1} I_0(\alpha L))} \begin{pmatrix} L^{-1} K_0(\alpha L) + \log \frac{L}{R} K_1(\alpha L) \\ \alpha I_1(\alpha L) K_0(\alpha L) + \alpha I_0(\alpha L) K_1(\alpha L) \end{pmatrix}. \]

To compute the probability \(p(x_0)\) we estimate two fluxes: first at the PSD given by

\[ J_{PSD} = \kappa \int_{\partial \Omega_{PSD}} u dS = 2\pi \kappa \int_0^L \frac{1}{D} K_0(\alpha r) r dr + 2\pi \kappa \int_0^L A I_0(\alpha r) r dr \]

and second the flux at the lateral boundary

\[ J_{Lat} = -2\pi D R \bar{u}'(R) = -2\pi D h C. \]

Thus the probability to hit one of the receptor, where the vesicle is released at the center is given by

\[ p = \frac{J_{PSD}}{J_{PSD} + J_{Lat}}. \]
General location of vesicular release.

To estimate the flux for a general location of vesicular release, we use the general expression of the Laplacian to rewrite equation (9),

$$\frac{\partial^2 \bar{u}(r, \theta)}{\partial r^2} + \frac{1}{r} \frac{\partial \bar{u}(r, \theta)}{\partial r} + \frac{1}{r^2} \frac{\partial^2 \bar{u}(r, \theta)}{\partial \theta^2} - \alpha^2 \bar{u}(r, \theta)\chi_{[0,L]} = -\frac{1}{rhD} \delta(r - r_0) \delta(\theta - \theta_0).$$

(12)

We chose the release point on the line $\theta_0 = 0$, the solution can be developed in a cosine series

$$\bar{u} = \frac{a_0}{2} + \sum_{n=1}^{\infty} a_n \cos(n\theta).$$

(13)

To estimate the flux, we shall compute

$$\kappa \int_0^{2\pi} \int_0^L \bar{u}(r, \theta) r dr d\theta = \kappa \int_0^{2\pi} \int_0^L \frac{a_0(r, r_0)}{2} r dr d\theta$$

By substituting the expansion (13) in equation (12) and integrating with respect to $\theta$ we found that $a_0$ satisfies

$$\frac{d^2 a_0(r|r_0)}{dr^2} + \frac{1}{r} \frac{da_0(r|r_0)}{dr} - \alpha^2 a_0(r|r_0)\chi_{[0,L]} = \frac{1}{D\pi hr} \delta(r - r_0).$$

(14)

We look for a solution of the form

$$a_0(r) = \begin{cases} A_1 I_0(\alpha r) & 0 < r \leq r_0 \\ A_2 I_0(\alpha r) + B_2 K_0(\alpha r) & r_0 < r \leq L \\ A_3 \log(r/R) & L < r < R \end{cases}$$

When $r_0 < L$, the continuity at the point $x_0 = (r_0, \theta_0 = 0)$ leads to

$$A_1 I_0(\alpha r_0) - A_2 I_0(\alpha r_0) - B_2 K_0(\alpha r_0) = 0$$

(15)

while integrating equation (14) over $(r_0 - \varepsilon, r_0 + \varepsilon)$, we obtain the condition

$$\int_{r_0-\varepsilon}^{r_0+\varepsilon} \frac{d}{dr} \left( r \frac{da_0(r|r_0)}{dr} \right) dr - \int_{r_0-\varepsilon}^{r_0+\varepsilon} \alpha^2 a_0(r|r_0) rdr = \frac{1}{D\pi h}$$

Taking the limit $\varepsilon \to 0$, we get that

$$A_2 I_1(\alpha r_0) - B_2 K_1(\alpha r_0) - A_1 I_1(\alpha r_0) = \frac{1}{\alpha D\pi hr_0}$$

(16)
The final condition comes from the interface $r = L$, where we require the continuity of $a_0$ and its derivative with respect to $r$. We get

$$A_2 I_0(\alpha L) + B_2 K_0(\alpha L) - A_3 \log(L/R) = 0$$
$$A_2 I_1(\alpha L) - B_2 K_1(\alpha L) - A_3 \frac{1}{\alpha L} = 0$$

From equations (15-17), we obtain four independent equations for the coefficients $A_1, A_2, B_2, A_3$ and the net flux can be expressed as

$$J_{PSD}(x_0) = \kappa \int_{\partial \Omega_{PSD}} u(r|x_0) dS$$

$$= \kappa \int_0^r (I_0(\alpha r), 0, 0, 0) \left( \begin{array}{cccc}
- I_0(\alpha r) & - I_0(\alpha r_0) & - K_0(\alpha r_0) & 0 \\
- I_1(\alpha r) & I_0(\alpha r_0) & - K_1(\alpha r_0) & 0 \\
0 & I_0(\alpha L) & K_0(\alpha L) & - \log(L/R) \\
0 & I_1(\alpha L) & - K_1(\alpha L) & - \frac{1}{\alpha L}
\end{array} \right)^{-1} \left( \begin{array}{c}
0 \\
0 \\
0 \\
0
\end{array} \right) rdr$$

$$+ \kappa \int_r^L (0, I_0(\alpha r), K_0(\alpha r), 0) \left( \begin{array}{cccc}
I_0(\alpha r) & - I_0(\alpha r_0) & - K_0(\alpha r_0) & 0 \\
- I_1(\alpha r_0) & I_1(\alpha r_0) & - K_1(\alpha r_0) & 0 \\
0 & I_0(\alpha L) & K_0(\alpha L) & - \log(L/R) \\
0 & I_1(\alpha L) & - K_1(\alpha L) & - \frac{1}{\alpha L}
\end{array} \right)^{-1} \left( \begin{array}{c}
0 \\
0 \\
0 \\
0
\end{array} \right) r dr.$$

In addition, the lateral flux is given by

$$J_{Lat}(x_0) = -2\pi DRh\bar{u}'(R) = -2\pi Dh A_3. \quad (18)$$

Thus the total probability to be activated one receptor when the neurotransmitters are released at position $x_0$ is given by

$$p(x_0) = \frac{J_{PSD}(x_0)}{J_{PSD}(x_0) + J_{Lat}(x_0)}. \quad (19)$$

In practice, we solve (15-17) numerically.

When a vesicle is released at a position outside the PSD, ($r_0 \geq L$), $a_0$ has the form

$$a_0(r) = \begin{cases} 
A_1 I_0(\alpha r) & 0 < L \leq r_0 \\
A_2 \log(r) + B_2 & L < r \leq r_0 \\
A_3 \log(r/R) & r_0 < r < R.
\end{cases}$$

Using similar considerations as previously, the continuity conditions lead to
the set of equations:
\[
\begin{align*}
A_1 I_0(\alpha L) - A_2 \log(L) - B_2 &= 0 \\
A_1 \alpha I_1(\alpha L) - \frac{A_2}{L} &= 0 \\
A_2 \log(r_0) + B_2 - A_3 \log \frac{r_0}{R} &= 0 \\
-\frac{A_2}{r_0} + \frac{A_3}{r_0} &= -\frac{1}{\pi Dh r_0}
\end{align*}
\] (20)

Solving the linear system (20), we obtain the following expression for the flux:
\[
J_{PSD}(x_0) = \int_0^L (I_0(\alpha r), 0, 0, 0) \left(\begin{array}{cccc}
I_0(\alpha L) & -\log(L) & -1 & 0 \\
\alpha I_1(\alpha L) & \frac{1}{L} & 0 & 0 \\
0 & \log(r_0) & 1 & -\log \frac{r_0}{R} \\
0 & -\frac{1}{r_0} & 0 & \frac{1}{r_0}
\end{array}\right)^{-1} \left(\begin{array}{c}
0 \\
0 \\
0 \\
\frac{1}{Dh r_0}
\end{array}\right) rdr
\] (21)

1.2 A partial absorbing boundary condition at the PSD

We present here our methodology to compute the partial absorbing constant \(\kappa\) for an ensemble of \(N\) partially reflecting receptors of size \(a\) located on the PSD. When a glutamate molecule hits a single receptor, it can sometimes be activated or not. This condition at a single receptor is given by a partial absorbing condition
\[
-D \frac{\partial p}{\partial n} = \kappa_a p
\]
where \(\kappa_a\) is the AMPA partially-reflecting activation barrier (\(\kappa_a = 0\) if there is no activation barrier and the receptor is activated upon a glutamate hitting while for \(\kappa_a = \infty\), the barrier would be so large that every glutamate molecule would only be reflected). The value of \(\kappa_a\) depends on the intrinsic properties of the AMPA binding site.

To compute \(\kappa\) the homogenized partial absorption coefficient, we consider that all the receptors are located in the PSD disk of radius \(R_{PSD}\). The general partial absorbing boundary condition would be
\[
-D \frac{\partial p}{\partial n} = \kappa \ p \quad \text{on the PSD.} \tag{22}
\]
Our criteria would be that the flux through the \(N_a\) individual receptor and the flux through the partially absorbing PSD should be equal. To compute the flux through the partial absorbing PSD, we solve the Mean First Passage
Time equation with the boundary condition \[ \text{22} \] instead of an absorbing boundary condition:

\[
D \Delta u = -1 \text{ on } \Omega \tag{23}
\]

\[
\frac{\partial u}{\partial n} = 0 \text{ on } \partial \Omega_r
\]

\[
-D \frac{\partial u}{\partial n} = \kappa u \text{ on the PSD}
\]

To solve this equation, we use the standard method involving the Neumann–Green function \((37, 38)\). In three dimensions, we find that mean first passage time to the PSD is approximated by

\[
u(x) \approx \frac{|\Omega|}{D} \left( \frac{1}{4R_{PSD}} + \frac{D}{2\pi \kappa R_{PSD}^2} \right) \tag{24}
\]

Thus the flux per particles is

\[
J = \frac{1}{u(x)} \approx \frac{D}{|\Omega|} \frac{1}{\frac{1}{4R_{PSD}} + \frac{D}{2\pi \kappa R_{PSD}^2}}.
\]

First let us consider the flux on \(N_a\) AMPA receptors of size \(a\) in a disk of size \(R\), which are fully absorbing. Then, the MFPT is

\[
\tau = \frac{|\Omega|}{4R_{PSD} D} \frac{N_a a + f(\sigma) R}{N_a a} \tag{25}
\]

Thus when we equal relation \[\text{25} \] with \[\text{24} \], we get the relation

\[
\frac{|\Omega|}{D} \left( \frac{1}{4R_{PSD}} + \frac{D}{2\pi \kappa R_{PSD}^2} \right) = \frac{|\Omega|}{4R_{PSD} D} \frac{N_a a + f(\sigma) R_{PSD}}{N_a a}
\]

which leads to the expression for the partial homogenization constant

\[
\kappa = \frac{D}{2\pi R_{PSD}^2 f(\sigma)} N_a a
\]

where \(f(\sigma) = 1 - \sigma\), \(\sigma = N_a a^2 / R_{PSD}^2\). Now in general, \([30, 40, 41]\), we obtain the following relation

\[
\tau = \frac{|\Omega|}{D} \left( \frac{1}{4R_{PSD}} + \frac{f}{N_a a} + \frac{D}{\kappa_a 2\pi a^2 N_a} \right)
\]

and thus

\[
\kappa = \frac{D}{2\pi R_{PSD}^2} \frac{f(\sigma)}{N_a a} + \frac{1}{\kappa_a 2\pi a^2 N_a} \tag{26}
\]
1.3 Comparison with Brownian simulations

Because our analytical analysis contains several approximations such as the averaging over the cleft height or the coefficients $A_1, A_2, B_2, A_3$ are approximated numerically, we evaluated the accuracy of our analysis by comparing the probability (19) with Brownian simulations (see figure 7). We simulated Brownian particles in the same cylindrical domain as the one used for the analytical computation with an absorbing lateral boundary condition. We put at the PSD a partial absorbing boundary with the condition $-D \frac{\partial p}{\partial n} = -\kappa p$. At the particle level, we implemented the reflection rule (38), in which particles hitting the PSD boundary are reflected with a probability

$$P = \frac{\kappa \sqrt{\pi}}{\sqrt{D}}$$

and absorbed with the complementary probability, where $D$ is the diffusion constant and $\Delta t$ is the time step of the simulation. The scheme is standard when the glutamate molecule is inside the cleft, but when $x(t) + \sqrt{2D} \Delta w < 0$ at the PSD, then we use

$$x(t + \Delta t) = \begin{cases} 
-(x(t) + \sqrt{2D} \Delta w) & \text{w.p. } 1 - P \sqrt{\Delta t} \\
\text{terminate trajectory otherwise.} &
\end{cases}$$

1.4 Estimation of the partial absorption rate $\kappa_a$ using experimental data.

Using a Markovian kinetic model for the initial binding step of a glutamate to an AMPAR, we estimate here the rate constant $\kappa_a$ and the homogenized coefficient $\kappa$ with the help equation 26.

In a two state chain model, accounting for binding and unbinding of a glutamate molecule to a receptor described as

$$C \xrightleftharpoons[k_{-1}]{k_1} O,$$  \hspace{1cm} (27)

the forward binding rate $k_1$ is given in units of Molar s$^{-1}$. In one hand, the binding rate is calculated by the flux formula as

$$J_{Markov} = k_1 A^{-1} N_g V^{-1} \int_{\partial \Omega_a} p(x) dx \approx k_1 A^{-1} N_g V^{-1} \pi a^2 p(x),$$  \hspace{1cm} (28)
where $A$ is the Avogadro number, $p(x)$ is the density of glutamate near the receptor and $V = \pi R h^2$ is the volume of the synaptic cleft. On the other hand, using the diffusion model, the flux term is given

$$J_{diff} = N_g \kappa_a \int_{\partial \Omega_a} p(x) dx \approx N_g \kappa_a \pi a^2 p(x), \quad (29)$$

where $a$ is the radius of a receptor and $\partial \Omega_a$ represents the receptor surface. By equating the two fluxes $J_{diff}$ and $J_{Markov}$, we obtain an expression for the partial reflecting constant

$$\kappa_a = k_1 A^{-1} V^{-1}.$$

Now, using the published value $k_1 = 10^7 M^{-1} s^{-1}$ (taken from [1]) we obtain that $\kappa_a \approx 1.06$. This two-model chain state is a good enough approximation even in the case where there are more states in the Markov chain. Indeed, the transition rates to desensitization states are lower than the open state so that in the short time scale, after binding (the time of interest in our model), the probable state is the open state.

### 1.5 Mathematical details for the computation of the partial rate $\kappa$

We provide here the mathematical detail used in appendix for the expression of the partial absorbing constant $\kappa$. We solve equation (23) asymptotically using the Green function:

$$\Delta_x N(x, y) = -\delta(x - y), \quad \text{for } x, y \in \Omega$$

$$\frac{\partial N(x, y)}{\partial \nu_x} = \frac{1}{|\partial \Omega|}, \quad \text{for } x \in \partial \Omega, \ y \in \Omega,$$

If $x$ or $y$ (or both) are in $\partial \Omega$, then only a half of any sufficiently small ball about a boundary point is contained in $\Omega$, which means that the singularity of Neumann’s function is $\frac{1}{2\pi |x - y|}$. The Neumann’s function for $y \in \partial \Omega$ is given by

$$N(x, y) = \frac{1}{2\pi |x - y|} + v(x, y),$$

where $v(x, y)$ is a regular function. Using Green’s identity and the boundary conditions (22), we obtain

$$u(y) - \frac{1}{D} \int_{\Omega} N(x, y) dx = \int_{\partial \Omega} N(x, y) \frac{\partial u(x)}{\partial \nu} dS_x + C,$$
where
\[ C = \frac{1}{|\partial \Omega|} \int_{\partial \Omega} u(x) \, dx. \]

The conservation of the flux leads (see (30)) to
\[ \int_{\partial \Omega_a} \frac{\partial u(x)}{\partial \nu_x} \, dS_x = -\frac{|\Omega|}{D}, \quad (30) \]

Following the argument in (39), the function \( N(x, y) \) is integrable independent of \( \partial \Omega_a \), whose integral is uniformly bounded, whereas \( C \to \infty \) as \( a \to 0 \).

Setting \( g(x) = \frac{\partial u(x)}{\partial \nu_x} \) for \( x \in \partial \Omega_a \) and using the boundary condition (22), we obtain the integral equation for the flux density \( g(x) \) in \( \partial \Omega_a \),
\[ -\frac{D}{\kappa} g(y) + \int_{\partial \Omega_a} N(x, y) g(x) \, dS_x = -C \quad \text{for} \quad y \in \partial \Omega_a, \]

Using the expansion of the flux \( g(x) = g_0(x) + g_1(x) + g_2(x) + \cdots \), where \( g_{i+1}(x) \ll g_i(x) \) for \( a \to 0 \) and choose
\[ g_0(x) = \frac{-2\alpha}{a\pi \sqrt{1 - \frac{|x|^2}{a^2}}}. \]

It was shown in, (38, 39) that if \( \partial \Omega_a \) is a circular disk of radius \( a \), then
\[ \frac{1}{2\pi} \int_{\partial \Omega_a} \frac{g_0(x)}{|x - y|} \, dS_x = \alpha \quad \text{for all} \quad y \in \partial \Omega_a. \]

Thus we approximate the solution by taking \( y \) at the origin, so that \( g_0(0) = \frac{-2\alpha}{a\pi} \), thus we get
\[ C = \left( \frac{2D}{\kappa \alpha \pi} + 1 \right) \alpha. \]

The flux condition (30) gives
\[ \int_{\partial \Omega_a} g_0(x) \, dS_x = -4\alpha \]

We conclude that
\[ u(x) \approx C = |\Omega| \left( \frac{1}{2\pi \kappa a^2} + \frac{1}{4Da} \right). \]
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Figure Legends

Figure 1.

Schematic representation of the Synaptic cleft. The synaptic cleft geometry is approximated as a narrow cylinder of height $h$ and the PSD is positioned at the center of the pre-synaptic terminal. We depicted a vesicle released at a distance $r_0$ inside the Active Zone (AZ). Diffusing receptors can either bind an AMPA receptor or diffuse away.
Figure 2.

The geometrical properties of the synaptic current. A. We decompose the synaptic current $I_S$ in a sum of 2, 3 and 4 glutamate bound glutamate molecules ($I_S = I_2 + I_3 + I_4$). In the range of 3000-9000 glutamates, the contribution of each configuration is $I_4 > I_3 > I_2$. The release is from the center. B. The synaptic current is plotted as a function of the release distance from the center of the synapse for one, two and three vesicles. In both graphs we used synapse of 500nm radius, height 30nm, PSD radius of 300nm.
Figure 3
Synaptic current (computed from [7]) versus the number of glutamate molecules. We show current Vs. the number of released glutamate molecules for different receptor radius, $a = 1.5\text{nm}, 1.8\text{nm}$ and $2\text{nm}$ . For receptor effective binding radius of $a = 1.8\text{nm}$ saturation achieved at four vesicles.
Figure 4.

**Optimal PSD radius.** A. The mean current and SD are plotted as a function of the PSD size for three different active zones (50 nm, 100 nm and 150 nm) (the synaptic radius is 500 nm and the height is 20 nm). B, C. The mean number of AMPA receptors bound by 2 (resp. 4) glutamate molecules as a function of the PSD radius. D. **Current vs. Active Zone radius.** The PSD size is fixed at 300 nm and each curve represents 1, 2 and 3 released vesicles. E. **CV vs. PSD size.** The CV achieves a minimum when the PSD and the active zone are approximately equal. In that case the Active Zone is 100 nm and the CV minimum is achieved for a PSD of radius of 120 nm. F. **Optimal PSD radius:** It is plotted as a function of the AZ radius obtained by minimizing the CV for a fixed AZ.
Figure 5

Synaptic current for different synapse radius. For a fixed active zone radius (50 nm), we plot the synaptic current as a function of the PSD radius for four different sizes of synapses 200, 300, 400 and 500 nm (the height is 30 nm). Doubling the size of the synapse leads to a current amplitude that increases from 125 to around 190 pA for a small PSD radius. (B) The CV is plotted as a function of the PSD radius: the CV minimum does not depend much on the synaptic radius. (C) The CV is plotted as a function of the PSD radius, for different number of released glutamate molecules. There is an optimal PSD size, and the CV decreases as a function of the number of released glutamate molecules. (D) We compare the CV as a function of the PSD radius curve when the number of released glutamate molecules is distributed according to a Gaussian distribution with a mean 3000 and a standard deviation of 500 (bold line) with a fixed number of 3000 glutamate molecules (dashed line). Fluctuation in the number of glutamate molecule in the vesicles does not affect much the general behavior of the CV with respect to PSD size.
Figure 6

A. MC Simulation For a fixed active zone radius (300 nm) a Monte-Carlo Brownian simulation of 500 molecules uniformly released from the AZ. Each experiment has 100 repetitions at different PSD size. B. CV analysis for a simple model. The model describes a random variable with three possible outcome values $I_1, I_2, I_3$. The probability function is given in (8). The model describes a single receptor with three conductivity levels, depends on the number of bound molecules, each can bind the receptor with probability $q$. Each curve represents the CV Vs. probability of binding $q$ with different values of $I_3$, where $I_1 = 1, I_2 = 2$ are fixed. For large values of $I_3$, an optimal point emerges. The existence of optimal CV as function of binding probability is thus strongly connected to the nonlinear cooperative effect of multi-binding.
Figure 7

Probability \( p(x_0) \) to bind a receptor before exit the cleft. We compare here the analytic solution of (19) (continuous line) with Brownian simulations (dots) in the cylindrical domain of radius \( R = 0.5 \), height 0.02. The radius of the PSD is \( L = 0.3 \).
Figure 1:
Figure 2:
Figure 3:
Multi-conductance AMPA receptor model

Figure 4:
Figure 5:
Multi-conductance AMPA receptor model

Figure 6:
Figure 7: