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REVIEW PAPER

The glutamatergic synapse: a complex machinery for information processing

Vito Di Maio[1]

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Abstract

Being the most abundant synaptic type, the glutamatergic synapse is responsible for the larger part of the brain's information processing. Despite the conceptual simplicity of the basic mechanism of synaptic transmission, the glutamatergic synapse shows a large variation in the response to the presynaptic release of the neurotransmitter. This variability is observed not only among different synapses but also in the same single synapse. The synaptic response variability is due to several mechanisms of control of the information transferred among the neurons and suggests that the glutamatergic synapse is not a simple bridge for the transfer of information but plays an important role in its elaboration and management. The control of the synaptic information is operated at pre, post, and extrasynaptic sites in a sort of cooperation between the pre and postsynaptic neurons which also involves the activity of other neurons. The interaction between the different mechanisms of control is extremely complicated and its complete functionality is far from being fully understood. The present review, although not exhaustively, is intended to outline the most important of these mechanisms and their complexity, the understanding of which will be among the most intriguing challenges of future neuroscience.

Keywords Glutamatergic synapse · Synaptic transmission · Synaptic modeling · Synaptic information processing · Brain information processing · AMPA · NMDA · EPSC · EPSP · dendritic integration · dendritic spines · LTP · LTD

Introduction

The brain is probably the most powerful information processing device we can imagine; it is capable of managing, in parallel, an incredibly huge amount of inputs that it integrates to produce coherent outputs. This powerful information processing device operates thanks to billions of connected processing units (the neurons) necessary to process the input information, determine its relevance and accordingly select what to store in memory traces, and produce the appropriate outputs. It is commonly accepted that neurons are the information processing units and the connecting system is formed by the synapses. Since their discovery by Sherrington (1906), synapses have been considered as simple structures necessary only to transfer signals from one neuron to another. Afterward, the subsequent studies on the synaptic structure and activity has shown that synapses are not merely bridges to transfer information, but they can manipulate information on different time scales and also possess several forms of plasticity. In the most recent years, neuroscientists have reconsidered the role of synapses in terms of information processing units with computational ability (among many others, see for example Abbott and Regehr 2004).

Neurons code information by sequences of stereotyped variation of the membrane potential (V_m) of $\sim 100\,\mathrm{mV}$ [namely, Action Potential (AP) or spike] emitted in a given time window ("neuronal code"), and each AP in the sequence is the elementary bit of neuronal information. Despite great effort spent both in experimental and computational studies, a definitive and clear interpretation of the "neuronal code" is far from being established, and it remains controversial if the code is embedded in the spike

To my parents, Giuseppe and Angela, who were my past and to whom I am in debt of my life and of my carrier and to my daughter Francesca which is my present and future.

✉ Vito Di Maio
vito.dimaio@cnr.it

[1] Institute of Applied Science and Intelligent Systems (ISASI) of CNR C/O Complesso Olivetti, Via Campi Flegrei 34, 80078 Pozzuoli NA Italy

rate (frequency) or the precise spikes occurrence into the sequence. (see for example, among many others Eggermont 1998; Lansky and Sato 1999; Kostal et al. 2007).

The APs sequence in a neuron is generated at the cone shaped region called the axon hillock, which emerges from the soma and then continue forming the axon, and it is generated thanks to the time-dependent integration of the synaptic inputs coupled to a threshold mechanism. The integration of the inputs produces a fluctuation of the value of V_m between a resting value ($V_m = V_r \sim -65\,\mathrm{mV}$) and a threshold one ($V_m = V_{th} \sim -55\,\mathrm{mV}$); a spike (or a sequence of spikes) is emitted every time V_m crosses the threshold value (i.e., $V_m \geq V_{th}$). To understand the nature of the "neuronal code", it is important to have a full understanding of the processes involved in synaptic transmission and on the integration of the synaptic inputs which permit to reach the threshold.

In the neocortex and hippocampus sub-fields (CA1 and CA3), $\sim 80-0\%$ of the synaptic inputs are of the excitatory type produced by pyramidal neurons release Glutamate (Glu) (Buhl et al. 1994; Gulyás et al. 1999; Megías et al. 2001; Merchán-Pérez et al. 2014) suggesting that glutamatergic synapses (Glut) play a major role in the information transfer and processing among neurons in these brain regions. Each single pyramidal neuron receives between 5×10^3 and 3×10^4 synaptic inputs and $80-90\%$ of them transfer the information carried by other pyramidal neurons by Glut type synapses (Buhl et al. 1994; Gulyás et al. 1999; Megías et al. 2001). The remaining $10-20\%$ are inhibitory synaptic contacts using γ-Amino-Butirric-Acid ($GABA_A$) as neurotransmitter (Buhl et al. 1994; Gulyás et al. 1999; Megías et al. 2001). It is, therefore, not surprising that Glut synapses have been identified as the most important support systems for reasoning, memory, and learning, which are abilities based on phenomena connected to synaptic plasticity like the Short Term Potentiation (STP), the Long Term Potentiation (LTP) and the Long Term Depression (LTD) (Larkman and Jack 1995; Martin et al. 2000; Beattie et al. 2000; Lu et al. 2001; Watt et al. 2004; Raymond 2007; Bourne and Harris 2011; Ahmad et al. 2012; Tabone and Ramaswami 2012; Bliss and Collingridge 2013; Hill and Zito 2013; Rey et al. 2020a). Moreover, their role in the cognitive processes have been confirmed by studies in which their malfunctioning has been associated with severe cognitive deficiencies (Volk et al. 2015) as Alzheimer (Sheng et al. 2012; Rudy et al. 2015; Serwach and Gruszczynska-Biegala 2019), Parkinson (Gardoni and Di Luca 2015), schizophrenia (Wu et al. 2018), autism (Rojas 2014; Huang et al. 2019) and attention-deficit/hyperactivity disorder (Lian et al. 2018).

Despite the apparent conceptual simplicity of the synaptic transmission, the Glut response to a presynaptic AP shows a large variability, and this variability depends on several control mechanisms (Di Maio et al. 2017; Di Maio 2019; Di Maio and Santillo 2020). In recent papers, to simplify, we proposed to divide the different mechanisms of control of the information flow in a Glut into presynaptic, postsynaptic, and extrasynaptic (for a general view on this aspect see, Di Maio et al. 2017; Di Maio 2019; Di Maio and Santillo 2020). This classification was inspired not only by the location of the mechanisms of control but also by the fact that LTP and LTD are often divided into pre and postsynaptic suggesting a different, but cooperative, role of the pre and postsynaptic neuron in the information flow control and memory formation (Larkman and Jack 1995; Lu et al. 2001; Raymond 2007; Lisman 2009; Castillo 2012; Ahmad et al. 2012; Bliss and Collingridge 2013; Yang and Calakos 2013; Rey et al. 2020a).

In pyramidal neurons, the postsynaptic response to a single bit of the presynaptic "neuronal code" (a single AP) is a depolarizing current named Excitatory Post Synaptic Current (EPSC) that locally modify the postsynaptic value of V_m producing a depolarizing wave named Excitatory Post Synaptic Potential (EPSP). Examples of simulated EPSPs and EPSCs generated locally at a Glut synapse are shown in Fig. 1.

Usually, in pyramidal neurons, a single AP produces at most the release of a single quantum (the content in Glu of a single vesicle) (Hessler et al. 1993; Hanse and Gustafsson 2001a). When a quantum is released, the molecules of Glu diffuse into the synaptic cleft where the binding to the α-amino-3-hydroxy-5-methyl-4-isoxazole (AMPA) and the N-Metil-Di-Aspartic Acid sensitive (NMDA) receptors, located postsynaptically, can occur causing their activation.

From the point of view of the information transfer, we can say that if a presynaptic AP is the elementary bit of the presynaptic neural code, then the EPSP should be considered its representation in the "synaptic code" (Di Maio 2019; Di Maio and Santillo 2020).

Differently from the AP, as visible in Fig. 1, the EPSPs are not stereotyped events, but they can vary in amplitude and time course. The EPSC registered for a unique synapse shows a coefficient of variation (C.V.) of 0.39 and 0.30 for the responses of AMPA and NMDA receptors, respectively. If computed among different synapses the C.V. range is $0.2-0.7$ for the AMPARs and $0.1-0.5$ for the NMDARs component (Clements et al. 1992; Liu et al. 1999; Ventriglia and Di Maio 2000a, a, b; Hanse and Gustafsson 2001a; Ventriglia and Di Maio 2002, 2003a; Franks et al. 2003). In terms of absolute amplitude, the EPSC peak has been found to vary from 5 pA to more than 100 pA in the same synapse (Bekkers et al. 1990; Raastad

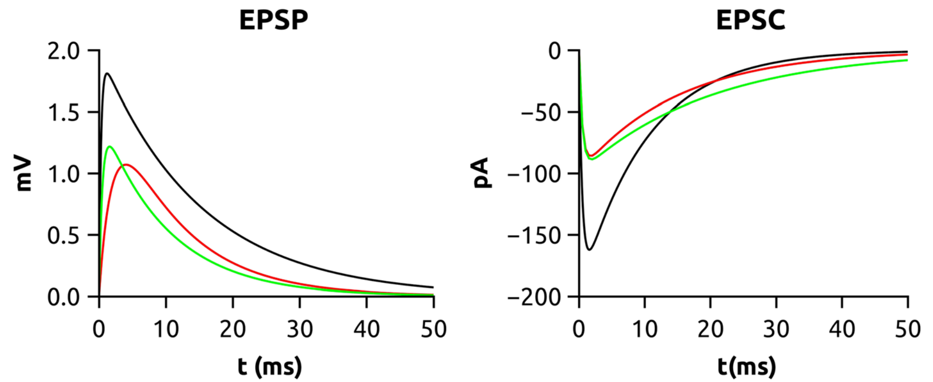

Fig. 1 Examples of simulated EPSPs and EPSCs

et al. 1992; Jonas et al. 1993; Schikorski and Stevens 1997; Liu and Tsien 1995; Forti et al. 1997; Magee and Cook 2000; Franks et al. 2003). This variability is the result of the integrated action of the several different mechanisms of control of the information flow that make the understanding and interpretation of the "synaptic code" even more challenging than the decoding of the "neuronal code".

The goal of the present review is to outline, in short, some of the sources of control of the information flow in Glut synapses.

The synaptic structure and diffusion of Glu

The interaction between the different components of the synaptic structure, which may vary among the synapses, and the diffusion of Glu into the cleft can play a significant role in shaping the postsynaptic response. The different position of the releasing vesicles (Dobrunz and Stevens 1997; Schikorski and Stevens 1997; Ventriglia and Di Maio 2000b; Murthy et al. 2001; Neher 2015) and the different number of molecules into the vesicle (Korn et al. 1993; Stevens and Wang 1995; Wall and Usowicz 1998; Prange and Murphy 1999; Ventriglia and Di Maio 2000a) contribute to shape the concentration profile of Glu into the synaptic cleft and then the synaptic response. Similarly, different structural organizations produce concentration profiles of Glu with diverse levels of interaction between the diffusing molecules and the receptors. For the above reasons, we propose to start with the description of the synaptic structure and the diffusion process of Glu in the synaptic cleft.

Glut synaptic structure

The fusion of a vesicle with the presynaptic membrane produces the formation of a fusion pore through which the Glu molecules are allowed to diffuse, by Brownian motion, into the cleft. The Brownian motion of Glu, both in the vesicle and in the cleft, is conditioned solely by the synaptic structures. Figure 2 shows a schematic and simplified representation of the Glut structure with, on the left, a diagram of the information control occurring at the different synaptic compartments.

In short, a Glut synapse is composed of the ending part of the axon (synaptic button) of the presynaptic neuron facing the head of a spine (a protruding segment) of a dendrite of the postsynaptic neuron. The presynaptic button contains vesicles filled with Glu and some of them are docked (yellow in the figure) and ready to release their quantum of Glu. Behind them, a set of vesicles form a reservoir system ready to replace the empty vesicles. Another pool (the largest one, not shown) is made of vesicles that undergo a filling procedure.

The area where vesicles are docked is called Active Zone (AZ) and is separated by a cleft of $\sim$20 nm from the postsynaptic area, where the AMPARs and NMDARs are co-localized to form the Postsynaptic Density (PSD). The pre and postsynaptic specialized areas are kept aligned by fibrils that contribute to increasing the synaptic efficacy (Zuber et al. 2005; Egles et al. 2007; Ventriglia 2011). This alignment is so important for the transfer of information that the lack or the simple misalignment has been associated with severe brain illnesses (Egles et al. 2007; Südhof and Malenka 2008). The fibrils form a sort of barrier which reduce the free diffusion of Glu out of the synaptic space (spillover) contributing to shaping the concentration profile into the cleft and then the postsynaptic response (see for example, Kruk et al. 1997; Ventriglia 2011; Chen et al. 2018; Haas et al. 2018).

At the postsynaptic side, the neck of the spine bridges the PSD to the dendritic branch forming the starting path for the information flow to the soma. The structure of the spine, its height, its diameters, the presence of voltage-gated channels, and, in general, its biophysical properties vary during brain development and in an activity-dependent manner. The spine properties are extremely influential in the control of the information transfer (see for example Bell et al. 2019, and Sect. 5.3).

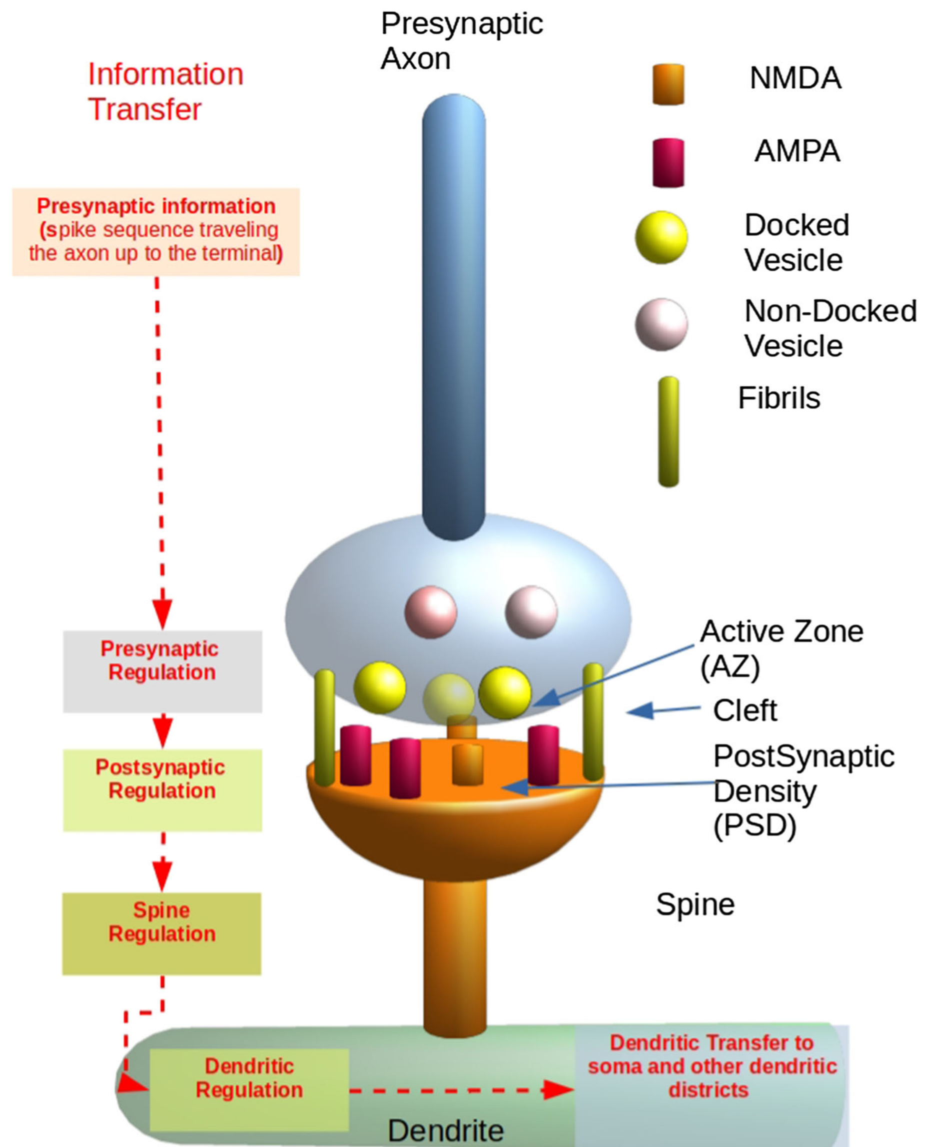

Fig. 2 Schema of a typical Glu Synapse. The red pathway shows the information flow

An additional, but external, component of the synaptic structure (not shown in the Fig. 2) are the glial cells (mostly astrocytes), located in the proximity of the cleft, which modulates the information transfer by simultaneously connecting the pre and postsynaptic side of the Glut synapse (see for example, De Pittà et al. 2011, 2012, and Sect. 6.2).

In summary, the dynamics of the quantum release operated by the vesicle is the principal mechanism of control of the presynaptic information flow (see Sect. 4.1). An additional modulation is operated by the synaptic structures (Ventriglia 2011) and by the glial cells surrounding the cleft (De Pittà et al. 2011, 2012; Allam et al. 2012). At the postsynaptic side, the key role is played by the receptors that can vary in number and characteristics (see Sect. 5.1) while the variability of the dendritic biophysical properties is the main factor producing extrasynaptic modulation of the information flow (see Sect. 6.1).

For a better understanding of the role of the different structures in shaping the postsynaptic event, it is worth preliminarily defining how the diffusion process of Glu occurs in the cleft.

Brownian diffusion of the Glu

The Brownian diffusion is, by definition, a random walk which, in the case of the Glut diffusion into the cleft, is limited only by the structures of the synapse. A general equation describing the diffusion process can be defined according to the Euler's schema (Guerrier and Holcman 2018)

$$\mathbf{X}(t+\Delta)=\mathbf{X}+\sqrt{D\Delta t}\eta \quad (1)$$

where $\mathbf{X}$ is the position of a molecule (x, y, z) in the $3D$ space, D is the diffusion coefficient (depending on the molecular mass and the absolute temperature), and η is a tridimensional random Gaussian vector.

Different authors used different approaches to simulate Brownian diffusion of Glu and probably the Monte Carlo Method has been the most widely used (Bartol et al. 1991; Faber et al. 1992; Stiles et al. 1996; Kruk et al. 1997; Glavinovic and Rabie 1997; Franks et al. 2002, 2003; Raghavachari and Lisman 2004). but some used different mathematical approaches (see for example, Kleinle et al. 1996; Ventriglia 2011; Ventriglia and Di Maio 2013a, a).

For the simulation of the synaptic activity, two main factors play a role in the choice of the simulation model: a good description of the synaptic geometry and the choice of an adequate time step. As said before, the simulation of synaptic geometry is crucial because the synaptic structures influence the diffusion dynamics and the evolution of the concentration time-course of Glu. The importance of the choice of the time step concerns the different time scales on which the synapse operates simultaneously. These two points have been discussed and approached differently by the authors (see for example: Holmes 1995; Clements 1996; Holmes 1995; Ventriglia and Di Maio 2000a, b, 2003b; Saftenku 2005; Ventriglia 2011; Ventriglia and Di Maio 2013a, b).

In the last version of our simulation system, we have improved the geometrical description of the synaptic space (Ventriglia 2011; Ventriglia and Di Maio 2013a, b). We have included the synaptic fibrils according to the description of Zuber et al. (2005) by considering them as cylinders with 14 nm of diameter and interspaced each other of 22 nm (Zuber et al. 2005; Ventriglia 2011; Ventriglia and Di Maio 2013a, b) positioned around the PSD. We have also considered the geometry of the receptors as cylinders of 14*nm* diameter protruding from the PSD of about 7 nm (Ventriglia 2011; Ventriglia and Di Maio 2013a, b). These improvements of the geometrical description have shown that the structural organization of the synapse does not play a marginal role in shaping the postsynaptic response (Ventriglia 2011; Ventriglia and Di Maio 2013a, b).

Simulation of Brownian diffusion is itself computationally very time-consuming, and this increases dramatically by increasing details in the description of the synaptic space. The choice of the time step is very crucial. It needs not to be too big, if a detailed description of the diffusion dynamics is necessary, and not too small because of the computational time required. For these reasons, the results of the larger part of the simulations are usually obtained by using time steps in the order of the microseconds or, in the best cases, of tens of nanoseconds. In our simulations, to gain the better possible results, we used probably the finest time step ever used [40×10^{-15} s (40 fs)] and no space discretization that is typical of the Monte Carlo Methods (Ventriglia and Di Maio 2000a, b, 2002, 2003a, b, 2013a, b; Di Maio et al. 2016a, b, 2018a, b, 2020). While to simulate the diffusion process the use of a 40 fs time step can give more precise results mostly on the interaction dynamics of Glu with receptors, it become senseless for the EPSC generation which needs to be compared with those experimentally obtained in the orders of milliseconds. For the occurrence of the EPSP, a time step of the order of the microseconds can suffice. To overcome this problem, we used two different self-made simulation programs, the first of which simulated the diffusion and binding of Glu to the receptors, and the second one, with a time step of 1 µs, was used, offline, to simulate the EPSP produced by the single Glut synapse (Ventriglia and Di Maio 2000a, b, 2002, 2003a, b; Ventriglia 2011; Ventriglia and Di Maio 2013a, b; Di Maio et al. 2016a, b, 2018a, b, 2020).

To simulate the Brownian diffusion process of Glu, we used the classical Langevin equations (Gillespie 1996) which in the general form can be written as

$$\frac{d}{dt}\mathbf{r}_i(t)=\mathbf{v}_i(t) \quad (2)$$

$$m\frac{d}{dt}\mathbf{v}_i=-\gamma\mathbf{v}_i(t)+\sqrt{2\epsilon\gamma}\Lambda(t) \quad (3)$$

where m is the molecular mass of Glu, $\mathbf{r}_i(t)$ and $\mathbf{v}_i(t)$ are respectively the position and velocity of the ith, $\gamma:\gamma=k_B\frac{D}{T}$ is a friction parameter which depends on the absolute temperature, on Boltzman constant (k_B) and on the diffusion coefficient of Glu (D), and Λ is a $3D$ Gaussian vector. For the numerical simulation, the following discretized forms were used

$$\mathbf{r}_i(t+\Delta t)=\mathbf{r}_i(t)+\mathbf{v}_i(t)\Delta t \quad (4)$$

$$\mathbf{v}_i(t+\Delta t)=\mathbf{v}_i(t)-\gamma\frac{\mathbf{v}_i(t)}{m}+\frac{\sqrt{2\epsilon\gamma\Delta t}}{m}\Omega_i \quad (5)$$

with Ω_i being a random vector with three Gaussian components (x, y, z) with $\mu=0$ and $\sigma=1$.

Different from several authors that start simulation assuming the instantaneous release of all the molecules (see for example, Clements 1996), our simulations have always started with all the molecules of Glu located inside a spherical vesicle. Once the vesicle fuses with the membrane cell, a pore of cylindrical shape is formed and starts to expand with an areal velocity. After the diameter of the pore exceeds that of a molecule of Glu, the molecules can enter the pore and pass into the cleft. Both the wall of the vesicle and that of the pore act as a reflecting boundary for

the hitting of the molecules. In the synaptic cleft, the hitting of a molecule to the presynaptic surface can produce, with low probability ($P_B \leq 10^{-4}$), the absorbing due to the possibility that it can be bound by a metabotropic presynaptic receptor. Except for the binding to a postsynaptic receptor and the crossing of the lateral surface of the synapse (considered as a cylinder too) all the synaptic structures (postsynaptic surface, fibrils, the external surface of the receptors) were considered as reflecting boundary. The lateral surface was considered as an absorbing boundary because, the high density of Glu receptors, located on the astrocytes that are strongly connected to the synaptic cleft (see Sect. 6.2), makes unlikely that a spilled over molecule of Glu will ever come back to the cleft.

The molecules of Glu were always considered massless (i.e., the volume was not considered), and therefore, the possible (but improbable) collisions among molecules were neglected. However, the molecular shape of the Glu was used, in the occurrence of approaching a binding site of an AMPA or NMDA receptor, to compute the binding probability by geometrical considerations. The classical mass equation used to compute the binding probability has no sense when a time step of 40 fs is used and the Glu concentration in the cleft is far from being stationary. For these reasons, we computed the binding probability by approximating the shape of a molecule of Glu to an ovoid that, to bind the receptor, has to enter a binding site of circular shape. We choose the ovoid form because the molecule of Glut is elongated and can bind a receptor only by its γ-carboxyl terminal group located at one end of the molecule. All the possible orientations of the γ-carboxyl group are inscribed in a sphere, while all the approaching angles useful for the binding process are inscribed in a cone angle; consequently, the binding probability was computed as the ratio between the cone angle and the sphere. Each receptor was assumed to have two binding sites for Glu located on the top of a cylinder. The positions of the receptors on the PSD were randomly chosen (Ventriglia 2011; Ventriglia and Di Maio 2013a, b; Di Maio et al. 2016a, b, 2018a, b, 2020).

The final output of the diffusion simulation were three 10×10 matrices:

(1) The identity matrix ($\mathbf{R}$), which identifies the receptor type on the PSD;

$$r_{(i,j)} \in \mathbf{R} = \begin{cases} 0 & ifnoreceptoratposition(i,j) \\ 1 & if\ r_{(i,j)} = AMPA \\ 2 & if\ r_{(i,j)} = NMDA \end{cases} \quad (6)$$

(2) the binding time of a first molecule of Glu to each receptor matrix ($\mathbf{B}_{\mathbf{t}_1}$)

$$t_{b1_{(i,j)}} \in \mathbf{B}_{t1} = \begin{cases} 0 & if\ r_{(i,j)} = 0ornoGluhasboundr_{(i,j)} \\ t & ifasingleGluhasboundthereceptorr_{(i,j)}attimet \end{cases} \quad (7)$$

and;

(3) the second molecule binding time ($\mathbf{B}_{\mathbf{t}_2}$) matrix.

$$t_{b2_{(i,j)}} \in \mathbf{B}_{t2} = \begin{cases} 0 & if\ r_{i,j} = 0\ or\ t_{b1_{(i,j)}} \geq 0\ andno\ 2^{nd}\ bindingof\ r_{(i,j)} \\ t & ifa\ 2^{nd}\ Gluhasbound\ r_{i,j}\ attimet \end{cases} \quad (8)$$

These matrices where used offline, by using a time steps of (1 μs), by a different simulation program to obtain the time course of the EPSP (Ventriglia 2011; Ventriglia and Di Maio 2013a, b; Di Maio et al. 2016a, b, 2018a, b, 2020).

Presynaptic information flow control

Probably it is not wrong to say that the presynaptic neuron "decides" what information to transfer and how to transfer it depending on its status. This "decision-making" procedure is operated by combining several presynaptic processes.

The most important part of the information flow control occurs in a domain space limited to $100nm$ in the proximity of the AZ (Guerrier and Holcman 2018) involving a complex system of proteins, which manage the docking and fusion processes, the distribution of voltage-gated calcium channels (VGCC), which trigger the release and, on a larger domain, the organization of the vesicles in pools and their mobility among the pools. Some of these processes directly or indirectly can modify the probability of release of a vesicle following a presynaptic AP inducing presynaptic forms of LTP and LTD (Raymond 2007; Branco et al. 2008; Lisman 2009; Castillo 2012; Rey et al. 2020a). Moreover, these mechanisms can shape the amplitude and time course of the single postsynaptic response.

Three different vesicle pools are present in the terminal button of an axon: (a) a readily releasable pool (RRP) consisting of 10–20 vesicles docked at the AZ; (b) a recycling pool formed of ~ 100 vesicles ready to replace those who have released their quantum, and; (c) a much larger pool of vesicles refilling of Glu which will move, once filled, to the recycling pool (Rizzoli and Betz 2004). Although a large variability may be observed among the different neurons, in general, $\sim 1-2\%$ of the total vesicles belong to the RRP, $\sim 10-20\%$ belong to the recycling pool, and $\sim 80-90\%$ to the reserve pool. The clustering in three pools, and the mechanisms of vesicle mobilization among the pools, requires the mediation of several proteins including synapsin, actin, and synaptotagmin (Rizzoli and

Betz 2004). The ultra-structural analysis of vesicle populations in the synaptic button, moreover, has shown, in some neurons, even more complex distributions (Schikorski and Stevens 1997, 2001) and variations of the dynamics of the vesicle mobility among the pools have been correlated to presynaptic LTP and LTD (Harris and Sultan 1995; Rey et al. 2020a, b). The proteins involved in the pools dynamics need rapid delivery and turnover which is operated thanks to a protein synthesis localized in the synaptic button (for a review, see Eyman et al. 2013; Crispino et al. 2014).

By considering the variability of the EPSP (the elementary bit of synaptic information), the first structural element to consider is the vesicle and its release mechanisms.

The vesicle

A vesicle can be approximated to a sphere filled with Glu. Takamori et al. (2006) have estimated that the vesicle membrane can contain up to 70 protein molecules the most abundant of which is synaptobrevin. The protein apparatus of vesicles is necessary for their dynamics, which includes the filling process, the movements among the different pools, the docking to the cell membrane, and finally, the formation of a pore. The main roles of the vesicle protein are their participation in the docking to the cell membrane and the pore fusion formation (Takamori et al. 2006).

The docked vesicles are distributed on the entire AZ and then each of them has different distance from the center of the synapse as well as a different content of Glu. The vesicle content and position are two important contributors to the variability of the synaptic response. If we consider a given number of molecules of Glu packed in a vesicle, the postsynaptic response will be variable depending on the distance of the vesicle from the central axis of the cleft. Different positions will, in fact, produce different concentration time course in the cleft (Ventriglia and Di Maio 2000a; Park et al. 2012). The maximal response is achieved by the release of a centrally located vesicle while the more peripheral ones will produce responses with amplitude proportionally lower as a function of the distance from the center because of the larger spillover of Glu (Ventriglia and Di Maio 2000a; Park et al. 2012; Kittel and Heckmann 2016). Some authors, however, have shown that the different positions correspond to diverse mechanisms of release: the so-called “kiss and run” and the “full fusion” mechanism (Fesce et al. 1994; Park et al. 2012). In the “kiss and run” mechanism the pore reverts its dynamics closing back fast after opening allowing only a partial release of the vesicle content while the “full fusion” releases the whole quantum because the vesicle membrane fully fuses with the neuronal one. According to Park et al. (2012), the vesicles positioned centrally use the “kiss and run” mechanism, and those peripherally located use the “full fusion” one. The full release of the vesicle content for the more peripheral vesicle should compensate for the amount of spillover due to their position producing approximately the same response of the vesicle centrally located in a sort of “vesicle democracy”. In some cases, however, the “kiss and run” mechanism (but also the “full fusion”) has been associated to multi-vesicular release (Korn et al. 1993; Prange and Murphy 1999; Boucher et al. 2010). Independently of the release mechanism, what is important for the present review is that the vesicle position combined with the mechanism of release and pore formation can be important causes of EPSP variability.

In addition to the position, vesicle content is not constant. Their diameter is variable and being almost spherical, a diameter variation of 10% produces vary the volume of almost 30% (Bekkers et al. 1990; Liu 2003; Schikorski and Stevens 2001) and then we expect to have a similar variation of the quantum content for the same concentration of Glu (Liu 2003). Moreover, it has been observed vesicle concentration of Glu varying in the ranges (60−210 mM) (Clements et al. 1992; Clements 1996; Choi et al. 2000; Liu 2003; Wu et al. 2007). The quantum variability, therefore, depends on the volume and concentration of Glu and in turn, on these two parameters, depends the concentration time course of Glu into the cleft. (Clements et al. 1992; Clements 1996; Choi et al. 2000; Lindau and Alvarez de Toledo 2003; Ventriglia and Di Maio 2003a, b). The Glu concentration time course and its clearance from the cleft, determine the binding probability of Glu to receptors, the binding duration, the receptor desensitization time, as well as the possibility that receptors located on PSD can be saturated or not (Clements et al. 1992; Clements 1996; Holmes 1995; Clements et al. 1998; Liu et al. 1999; McAllister and Stevens 2000; Ventriglia and Di Maio 2000a, b; Ventriglia 2004).

There is no agreement, among the authors, on the number of molecules of Glu forming a quantum. The differences arise mainly because of the different estimations of the internal volume of the vesicle and the experimental data set used. For example Clements (1996) carried his simulations assuming an instantaneous release of ~ 3000 molecules while we have estimated that the correct number should be less than 1000 (Ventriglia and Di Maio 2000b). Our computation was based on data by Schikorski and Stevens (1997) by considering an inner radius ranging 9.9−13.3 nm and a mean concentration of 140 mM. We considered that larger radii used by other authors could be due to a wrong estimation of the shrinkage effect on the membrane thickness due to the electron microscopy fixation protocols (Ventriglia and Di Maio 2003a). Other authors have obtained different values either for the Glu

concentration (0.4 M (Karunanithi et al. 2002)) and for the estimation of the internal radius and simulation have been made with 2000 molecules of Glu (Franks et al. 2003, based on data of Karunanithi et al. (2002) obtained on *Drosophila*). The results of our simulation have shown that, for a vesicle releasing centrally, and a number of AMPA and NMDA receptors expected on a hippocampal mean size synapse, (total 68: AMPARs = 55, NMDARs = 13 (Ventriglia and Di Maio 2013a, b; Di Maio et al. 2018a)), saturation of receptors could easily occur if quantum exceed 1000 molecules and saturation has been excluded in many experimental and computational studies (Holmes 1995; Liu et al. 1999; McAllister and Stevens 2000; Ishikawa et al. 2002; Yamashita et al. 2003; Ventriglia 2004). For this reason, we have always used less than 800 Glu molecules to obtain an EPSC close to the mean value obtained by Forti et al. (1997) ($\sim$25 pA at hippocampal synapses).

Independently of the quantum content and the simulation diffusion model used, the difference in content and position among the docked vesicle is a significant source of EPSP (EPSC) variability (Bekkers et al. 1990; Faber et al. 1992; Jonas et al. 1993; Korn et al. 1993; Wall and Usowicz 1998; Prange and Murphy 1999; Auger and Martin 2000; Hanse and Gustafsson 2001a; Sahara and Takahashi 2001; Karunanithi et al. 2002; Ventriglia and Di Maio 2002; Franks et al. 2003; Ventriglia and Di Maio 2003a; Liu 2003; Raghavachari and Lisman 2004; Wu et al. 2007). If we combine the the release method ("kiss and run" or "full fusion"), the vesicle content and position, also excluding the post and extrasynaptic sources of variability, the variability observed in the simulations can cover almost the full range of that observed experimentally (Ventriglia and Di Maio 2000a, b, 2002, 2003a, b; Park et al. 2012).

An important open question in this context is if for the release of a single quantum following an AP, the position and the number of Glus into the releasing vesicle depend on stochastic processes or if, among the different docked vesicles, a specific one is chosen that better fits the information to transfer. Moreover, since the quantum release is involved in presynaptic LTP and LTD, an additional question is: "how the above (stochastic?) processes can contribute to these phenomena?". To answer these questions, probably some suggestions can be obtained from the studies of the mechanisms of docking and pore fusion of the vesicles.

The vesicle release mechanism

It is largely accepted that the probability of release of a vesicle following a presynaptic AP is <1. Moreover, several authors have shown that this probability increases with specific presynaptic activity producing a form of presynaptic LTP (see for example Hanse and Gustafsson 2001a, b; Millar et al. 2002; Dobrunz 2002; Raymond 2007; Castillo 2012; Yang and Calakos 2013; Guerrier and Holcman 2018; Rey et al. 2020a, among many others). The quantum release probability, therefore, is a key parameter for the "neuronal code" transfer between two neurons because it determines the transfer of every single bit of information as well as for memory processes connected to presynaptic LTP and LTD. The release probability is strongly connected to the vesicle trafficking and the functionality of the docking machinery and fusion pore.

The docking and fusion of vesicles at the presynaptic membrane is allowed by the action of the soluble N-ethylmaleimide-sensitive fusion attachment protein (SNARE) that forms a specific machinery which functionality is not fully clarified (among many others see, Ramakrishnan et al. 2012).

On each vesicle, there is a SNARE complex (v-SNARE) to whom the synaptobrevin participates with important roles (Söllner et al. 1993). On the plasma membrane, syntaxin and a synaptosomal-associated protein (for example SNAP-25) have a key role in the formation of the target SNARE complex (t-SNARE). A docking event occurs when a v-SNARE complex of a vesicle meets a t-SNARE on the membrane forming a four-helix stable complex, often named "SNAREpin" (Sutton et al. 1998; Weber et al. 1998; Li et al. 2007). This complex catalyzes the event of fusion by lowering the energy barrier (Ramakrishnan et al. 2012; Li et al. 2007). An oversimplified schema of the configuration is visible in Fig. 3.

It is not the goal of the present review to analyze the complexity of the interactions of the SNARE complexes. What is of interest here is to outline that the vesicle release probability depends on Ca^{2+} sensors, present on the intracellular part of the SNAREpin, that are activated by an inward Ca^{2+} current following an AP (see Fig. 3).

Probability of release, in fact, is highly correlated with the amplitude of transient Ca^{2+} currents in the pyramidal neurons of the cortex (Rozov et al. 2001; Koester and Johnston 2005) and of the hippocampus (Holderith et al. 2012; Éltes et al. 2017). The Ca^{2+} current is due to the activation of the conductance mediated by Voltage-Gated Calcium Channels (VGCCs). These channels usually are of type $Ca_v2.2$ (Ramakrishnan et al. 2012) and are located in the proximity of the AZ in a radius of 100 nm. Because the free Ca^{2+} undergoes to fast intracellular buffering (95% of intra-cellular Ca^{2+} is buffered) the efficacy of these channels in triggering a release is restricted to sub-domains of 10–20 nm in the proximity of the vesicle (Sabatini and Regehr 1999; Beaumont et al. 2005; Guerrier and Holcman 2018). The number, density, and position of the VGCCs

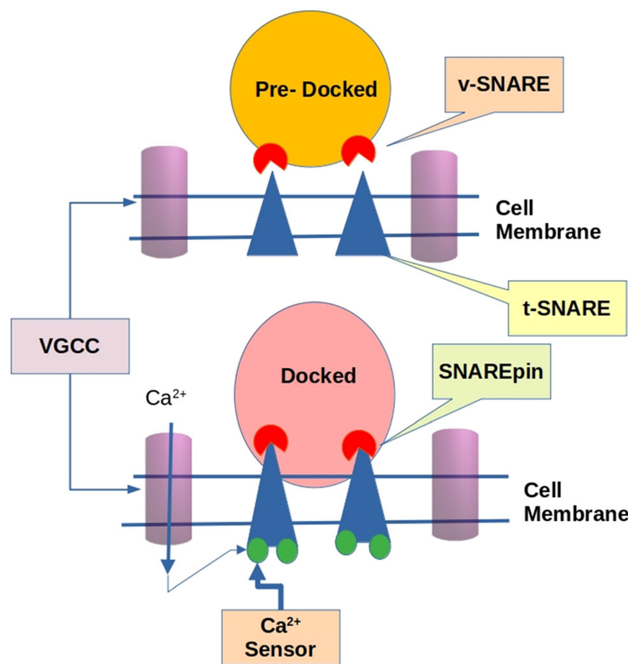

Fig. 3 Simplified schematic representation of the SNARE complex configuration and vesicle docking

around each vesicle are crucial factors determining the release probability which depends on the binding of a sufficient number of free Ca^{2+} ions to the SNARE sensors (Rozov et al. 2001; Koester and Johnston 2005; Vyleta and Jonas 2014; Nakamura et al. 2015; Fekete et al. 2019). The Synaptotagmin I, which participates both in the docking and the fusion pore processes, has 4–5 Ca^{2+} binding sites and seems to be the operational units for the triggering of these processes (Chapman 2002). It can be argued that this protein could determine the probability of release depending on the number of Ca^{2+} ions bound to its sensors.

The probability that a free Ca^{2+} ion interact with a sensor of the SNARE complex is strongly connected to the fast and transient increases of the Ca^{2+} concentration in the proximity of the sensor. The distribution of VGCCs (clustered or uniform), and that of the vesicles (crowded or sparse) on the AZ, shape the Ca^{2+} concentration in the proximity of the sensors and, consequently, the probability of a quantum release following an AP (Rozov et al. 2001; Koester and Johnston 2005; Vyleta and Jonas 2014; Nakamura et al. 2015; Fekete et al. 2019). In summary, we can say that the higher the density of VGCC around a vesicle, the higher is the level of Ca^{2+} concentration in its micro-domain and the probability of release.

The probability of release of a single quantum following an AP has been estimated to vary between 0.2 and 0.91 and the increases of this variability seem to be connected to presynaptic LTP. The fact that it is rarely 1 says that it is unlikely that the "neural code" is ever mirrored in a fully corresponding "synaptic code". It has also been shown that variabilities of the two codes do not co-vary Hanse and Gustafsson (2001b). Moreover, the possibility that these probability increases in an activity-dependent way suggest that the presynaptic LTP could be connected to an improvement of the code transfer among the neurons.

The molecular structure of the opened pore and its dynamics are another important factor capable of shaping the postsynaptic response (see for example Burgoyne 2000; Lindau and Alvarez de Toledo 2003; Marrink and Mark 2003; Ventriglia and Di Maio 2003b; Lai et al. 2013; Fuhrmans et al. 2015). The role of the SNARE complex and the dynamics of the pore formation are still a matter of debate and several points need clarification (Lai et al. 2013; Fang and Lindau 2014).

Summary of presynaptic information flow control

The presynaptic neuron regulates the information to transfer essentially by two main mechanisms: one acting on the single bit of information (EPSP) and another on the "neuronal code" to transfer. The modulation on the single EPSP is mediated by the Glu concentration time course in the cleft which depends on the number of molecules inside the vesicle, by its position on the AZ, by the dynamic of the fusion ("kiss and run" or "full fusion"), and by the density and number of the structures (fibrils and receptors) present in the synaptic cleft.

The modulation of the "neuronal code, depends on the quantum release probability following each single AP forming the code. Also, if the release probability increases in an activity-dependent manner (presynaptic LTP) the "synaptic code" will change in an activity-dependent manner but will rarely reproduce the complete presynaptic AP sequence.

Postsynaptic information flow control

Being the elements producing the postsynaptic response, AMPA and NMDA receptors are the main actors of the postsynaptic information control. Their structural organization, the single-channel conductance, their total number, the proportion AMPARs/NMDARs, and their activation/deactivation dynamics are all factors concurring in shaping the single postsynaptic event. Also, the size of the PSD (and that of the synapse) depends on the number of receptors that vary during maturation but also among the different synapses. LTP and LTD depend on the variation of the number of receptors (mainly AMPARs) and the size of the synapse depends on the number of receptors as well. The increasing size of synapses directly increases the cleft

volume modifying the concentration time course of Glu with the obvious effects on the response illustrated above.

The postsynasptic density: AMPA and NMDA receptors

The modern techniques of molecular biology and the possibility to clone the receptors have permitted great advancements of the studies on the composition, properties, and dynamics of both AMPA and NMDA receptors (see for example, among many others, Lu et al. 2009).

AMPA and NMDA receptors are cation-selective ion channels that are activated by Glu. They are formed of different protein subunits, the diverse assembly of which produces receptors with different affinity for Glu, different binding probability, different desensitization periods, and different conductances (Dingledine et al. 1999; Lu et al. 2009).

AMPARs can be formed as homo- or hetero-tetramers, which means they can be composed of four identical (homo) or different (hetero) subunits, of the following type GluR1, GluR2, GluR3, and GluR4 (or GluR A-D). The electrical conductance, and therefore the AMPARs contribution to the total EPSC (EPSP), depends on the subunit composition (Dingledine et al. 1999; Jonas 2000; Safferling et al. 2001; Cull-Candy et al. 2006; Isaac et al. 2007; Midgett and Madden 2008; Lu et al. 2009). The most commonly accepted form of LTP (postsynaptic LTP) depends on the activity-dependent increase of the AMPARs conductance mainly due to the increased number of AMPARs on the PSD, but also to the modification of their tetrameric composition (Benke et al. 1998; Isaac et al. 2007).

AMPARs are channels permeable to Na^+ and K^+ and, in general, they are considered not permeable to Ca^{2+} although AMPARs lacking the GluR2 subunit have been shown permeability to Ca^{2+} too. The GluR2-lacking AMPARs have a larger single-channel conductance and can be blocked in a voltage-dependent manner by endogenous polyamines (Cull-Candy et al. 2006; Midgett and Madden 2008). The larger portion of AMPARs in the brain have GluR2 subunits but some evidence suggests the presence of Ca^{2+}-permeable AMPARs correlated with phenomena of plasticity (Cull-Candy et al. 2006; Midgett and Madden 2008).

Although in the past some authors have inferred a pentameric organization for NMDA receptors consisting of three GluN1 and two GluN2 subunits (Premkumar and Auerbach 1997), more recent studies have shown that NMDARs are necessarily heterotetramers composed of 2 copies (a dimer) of subunits called GluN1 and a dimer of GluN2 (Sanz-Clemente et al. 2013; Karakas and Furukawa 2014) or GluR3 (Sanz-Clemente et al. 2013). However, the simultaneous presence of GluN1 and GluN2 seems to be necessary for the opening of the channel, and variants of GluN1 and GluN2 can produce different dynamics of the channel pore formation (Mcilhinney et al. 2003; Sanz-Clemente et al. 2013; Karakas and Furukawa 2014; Scheppach 2016; Sun et al. 2017). Also for the NMDA receptors, the biophysical properties depend on the subunits composition (Dingledine et al. 1999; Jonas 2000).

The main functional difference with the AMPA receptors is that the conductance of the NMDA receptors at the resting potential ($V_m = V_r \sim -65\,\mathrm{mV}$) is blocked by Mg^{2+} and then the Glu binding is a necessary but not sufficient condition for their activation. The strength of the Mg^{2+}-block depends on the subunits composition. For example, the variants GluN1/2A and GluN1/2B are more strongly blocked than GluN1/2C and GluN1/2D (Monyer et al. 1992; Kuner and Schoepfer 1996; Qian et al. 2005). Removal of the block is voltage-dependent and the removal of Mg^{2+} is achieved only by sufficient membrane depolarization. The removal can be fast or slow depending on the subunit's composition.For example, GluN1/2A and GluN1/2B receptors undergo a fast removal while GluN1/2B receptors to a slow one (Clarke and Johnson 2006). When activated, NMDARs are permeable to Ca^{2+} and are connected directly to intracellular mechanisms Ca^{2+}-dependent which regulate both the AMPA expression and their number on the PSD. The voltage-dependent activation and the Ca^{2+} permeability assign a role to the NMDARs quite different from that of the AMPARs because they not only participate in shaping the single synaptic response but activate phenomena like LTP and LTD.

However, we can say that the total number of receptors, the type, and their relative proportion shape the EPSP (EPSC) of the Glut synapse.

The synaptic response

The excitatory postsynaptic response consists of a depolarizing current (EPSC) generated accordingly to the equation

$$I_{syn}(t) = G_{syn}(t)(V_m(t) - V_{rev}) \tag{9}$$

where I_{syn} is the EPSC, G_{syn} is the synaptic conductance, $V_m(t)$ is the membrane potential and V_{rev} is the synaptic reverse potential (-10–$0\,\mathrm{mV}$ for Glut synapses).

Due to the different activation procedures and properties between the AMPA and NMDA receptors, their contribution to the EPSC is diverse. Since the sufficient condition to activate the AMPARs is the binding of two molecules of Glu and, because of their activation dynamics, the AMPARs give a fast-rising response (peak <0.5 ms) with

a fast decay (~ 10 ms) while NMDA response, when exists, usually rises slower but is much more prolonged in time (in some cases more than 100−200 ms (Clements et al. 1992)). An example of AMPA-EPSC and one of NMDA-EPSC, simulated by the difference of two negative exponentials (see below), are shown in Fig. 4.

The most important parameters contributing to the response variability on the postsynaptic side are the number, the proportion, and the distribution of receptors on the PSD (Takumi et al. 1999; Allam et al. 2015). For a given quantum of Glu released, the number and type of receptors, their composition in subunits, and their organization on the PSD determine the values of G_{syn} in Eq. (9).

In Glut synapses usually, the number of NMDARs is constant or it varies little as a function of the activity (Watt et al. 2004), while that of AMPARs varies in an activity-dependent manner. For example, new forming synapses often have no AMPA response (AMPA silent synapses) but the response increases during maturation thanks to the insertion of new AMPARs following the NMDARs activation (Wu et al. 1996; Hanse et al. 2013). In Glut synapses of the hippocampus, the number of AMPARs has been shown to vary between 3 and 140 Nusser et al. (1998). In our simulations, for a mean size synapse of the hippocampus, we have considered reasonable the number of 55 AMPARs (Ventriglia and Di Maio 2013a, b; Di Maio et al. 2018a, b). The activity-dependent increases of the number of AMPARs is not only a phenomenon of synaptic maturation but is considered the most important mechanism of postsynaptic LTP induction (among many others, Larkman and Jack 1995; Malinow and Malenka 2002; Collingridge et al. 2004; Watt et al. 2004; Nicoll and Schmitz 2005; Rao and Finkbeiner 2007; Raymond 2007; Lau et al. 2009; Ahmad et al. 2012; Bliss and Collingridge 2013; Baudry et al. 2015).

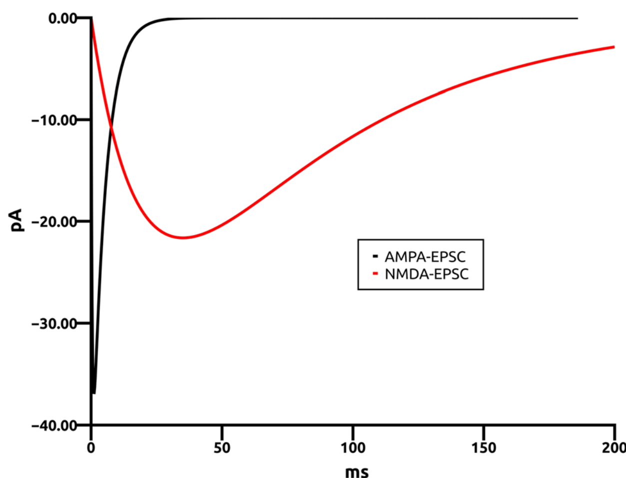

Fig. 4 Simulated AMPA-EPSC (black line) and NMDA-EPSC (red line)

The NMDA-Mg^{2+} block, being voltage-dependent, is not only a system modulating the single EPSP but is crucial because it determines what kind of information has to be memorized in the short or long term (plasticity). Only the information connected to a sufficient excitation generates the appropriate depolarization at the level of the PSD capable to unblock the NMDARs-Mg^{2+} permitting the Ca^{2+} inward current necessary to switch on the intracellular cascades which can produce new AMPARs insertion on the PSD (postsynaptic LTP) (Lau et al. 2009; Baudry et al. 2015, see for example).

To have the full contribution of the NMDARs conductance (all receptors unblocked), the level of depolarization has to reach a value of $V_m \geq +40$ mV (Jahr and Stevens 1990; Vargas-Caballero and Robinson 2004). For a given cleft concentration of Mg^{2+}, in the interval of $-65\,\text{mV} < V(t) \leq +40$ mV, the relationship G_{NMDA}/V_m follows a sigmoid function (Jahr and Stevens 1990; Vargas-Caballero and Robinson 2004). By using the normalized form of this dependence in terms of unblocking probability, we have shown that the fast activation of AMPARs can produce a local variation of V_m such to activate (partially) the NMDARs conductance which can give a contribution to the amplitude, time to peak and time course of the total EPSP. This form of AMPARs/NMDARs cooperation can be variable and this variability can be considered another modulation of the system of the synaptic information transfer (Di Maio et al. 2016a, b).

An additional mechanism of AMPARs/NMDARs cooperation (not considered in our simulations), seems to be their specific position on the PSD. Some studies have shown that the position of the receptors on the PSD is not random (as we have assumed in our simulations) but there is a sort of clusters organization which optimize the synaptic response (Nair et al. 2013; Tang et al. 2016; Choquet 2018).

AMPARs/NMDARs cooperation strongly depends on the biophysical properties of the spine and mostly on its total impedance. A variation of V_m, such as to allow the partial NMDARs recruitment, is possible only for the high input impedance of the spine (Rall 1974) that produces a large depolarization of V_m for the small current produced by the AMPARs. The large input impedance is not the only of the spine biophysical properties that contributes to the information flow control.

The spine and the information flow control

Structurally, the spine can be divided into a neck and a head on the top of which the PSD is allocated. However, it is not a passive scaffold for the PSD but it is a specialized chemical and electrical compartment that separates the

synapse from the rest of the neuron (Rall 1974; Rall and Rinzel 1973; Tønnesen et al. 2014). From the electrical point of view, the spine is considered as a separate circuit connecting the synaptic circuitry with the dendrite (Tønnesen et al. 2014; Burk et al. 2017, see for example).

The biophysical properties of the spine influence the value of $V_m(t)$ and, hence, the driving force contributing to shaping the EPSP.

Spines are essentially micro-segments protruding from dendrites. From the micro-anatomical point of view, it is possible to identify several types of spine and the differences among them have been associated with different degrees of synapse maturation and functionalities. For example, the so-called filipodia have a height twice its width and are considered as newly formed synaptic contacts (Yoshihara et al. 2009). The so-called "mushrooms", instead, have a thin neck and a head formed as a bulb and has been associated with synaptic maturation (Nimchinsky et al. 2002; Sala and Segal 2014) but also to LTP because the insertion of new AMPA receptors, associated with this phenomenon, seems to be responsible for the mushroom morphology (Matsuzaki et al. 2001, 2004; Bosch et al. 2014). On the contrary, the spine shrinkage is associated with the loss of AMPARs and the consequent LTD (Zhou et al. 2017).

The neck of the spine is the first part of the EPSP trip to the soma and, therefore, it is extremely important in controlling the information flow (Araya et al. 2006, 2007, 2014; Tønnesen et al. 2014; Acker et al. 2016; Jayant et al. 2016; Kwon et al. 2017).

Two main factors, interconnected with each other, determine the electrical properties of the neck: (a) its electrical resistance, which depends on its diameter and; (b) the presence of voltage-gated ionic channels.

About the electrical resistance, different authors have obtained different results, difficult to compare each other, mostly because of the different methods used and different synapses investigated. For example, in the hippocampus regions, while Tønnesen et al. (2014) have estimated a typical resistance of $\sim 60\,\mathrm{M}\Omega$, Harnett et al. (2012) have estimated a possible range of $400-600\,\mathrm{M}\Omega$. Spruston (2008); Acker et al. (2016), with two different methods, have estimated respectively a mean neck resistance of $179\,\mathrm{M}\Omega$ in a range $23-420\,\mathrm{M}\Omega$ and $204\,\mathrm{M}\Omega$ in a range $52-521\,\mathrm{M}\Omega$ in different areas. Other authors (for example, Rall 1974) have estimated input resistance of the spine in the order of the $G\Omega$s. Functional variations, however, can occur (also transiently) depending on several factors because the diameter of the neck can vary (for example thanks to osmotic factors following the influx of Ca^{2+}). A relationship between the variation of the neck diameter and its resistance has been described by Palmer and Stuart (2009). Diameter variation from 0.23 to 0.051 μm implies a resistance variation from $25\,\mathrm{M}\Omega$ to $500\,\mathrm{M}\Omega$ and one from 0.4 to 0.004 μm a variation from $10\,\mathrm{M}\Omega$ to $84G\Omega$ (Palmer and Stuart 2009).

The whole spine electrical compartment can be very complicated when considering all the possible sub-components (neck, dendrite, PSD, etc.) and every single variation of the properties of any of the sub-component can produce some significant influence in shaping the information transferred to the dendrite. However, when considering the single EPSP, the real important factor is that the current flowing through the neck resistance produces a final variation of potential in the proximity of the PSD influencing the EPSC amplitude according to Eq. (9). For this reason, in our simulations, we have considered a simplified model of the spine circuitry (see Fig. 5) which privileges the resistive components and considers essentially the contribution of two in series resistances that summing up give a final value of $600\,\mathrm{M}\Omega$ ($100\,\mathrm{M}\Omega$ for the neck and $500\,\mathrm{M}\Omega$ for the protein structure of the PSD) (Di Maio et al. 2016a, b, 2018a, b, 2020).

By this simplified model, we have shown that variations of the PSD input resistance can modulate the number of the NMDARs recruited following the fast AMPARs activation in a sort of cooperation among the two receptor types (Di Maio et al. 2016a, b).

For our goal, the importance of the neck stays in modulating the information flow from the synapse to the soma and from the dendrites to the PSD contributing to the

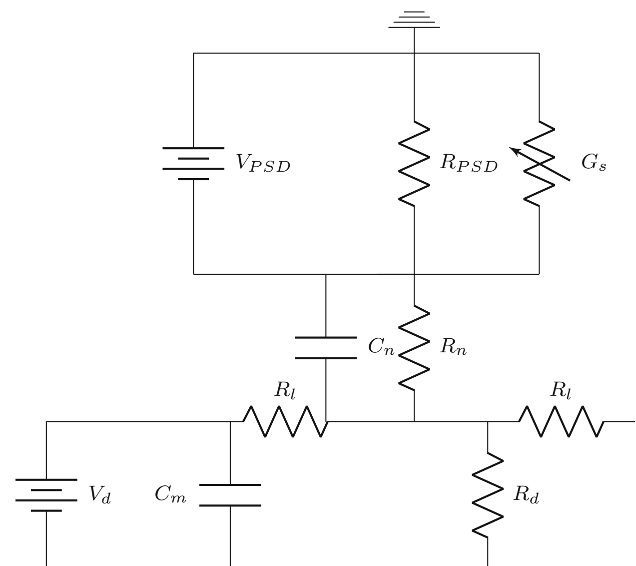

Fig. 5 Simplified electrical circuit of the spine and its connection to the dendrite. V_{PSD} is the difference of potential at the level of the PSD, V_d is the difference of potential at the level of the dendrite. R_{PSD} is the input resistance at the PSD, R_d is the dendrite resistance and R_l is the longitudinal resistance of the intracellular liquid into the dendrite. R_n is the neck resistance and C_m the membrane capacitance

properties of every single EPSP. However, to be more accurate, this contribution is not only due to the neck properties but to the bioelectrical interaction between the spine and the dendrite where the synapse is allocated. In this context, for example, the relationship between the spine circuitry and the dendritic properties, have shown a strong relationship with the difference between the EPSP amplitude at the origin (13 mV in a range 6.5–30.8 mV) and the soma ($\sim$0.59 mV) on average) (Spruston 2008; Acker et al. 2016) and these results well agree with our modeling results (Di Maio et al. 2016a, b).

The presence of voltage-gated calcium channels (VGCC) (Sabatini and Svoboda 2000; Sabatini et al. 2002; Bloodgood et al. 2009; Lau et al. 2009; Hu et al. 2018) and possibly Na^+ voltage-gated channels (Tsay and Yuste 2002, 2004; Araya et al. 2007) dramatically modify the properties of the neck and its ability to carry information. The activation of these channels occurs thanks to transient modifications of V_m due to the backpropagation of AP into the dendrites or to the coincident firing of several synapses located in the same dendritic area (see for example, among many others, Palmer and Stuart 2009; Di Maio et al. 2018a; Lau et al. 2009; Di Maio et al. 2018b, 2020). Depolarization of the membrane induced by the activation of voltage-gated channels of the spine has two contrasting effects. On one side the increasing of $V_m(t)$ at the level of the PSD reduces the driving force (see Eq. (9)) reducing the current produced by AMPARs but, on the other side, it increases the probability of Mg^{2+}-NMDARs unblocking contributing to increase the NMDARs component of the EPSC and directly influencing the occurrence the synaptic plasticity (Di Maio 2008; Di Maio et al. 2018a, b; Di Maio 2019; Di Maio et al. 2020; Di Maio and Santillo 2020).

From what is said above, we can infer that the flow of information from the synapse to the soma is not a one-way street but can be bi-directional influencing directly the EPSP amplitude and then the “synaptic cosw” (Rall 1974; Gulledge et al. 2012; Di Maio et al. 2018a, b, 2020).

Summary of postsynaptic information flow control

In summary, several biophysical properties of the postsynaptic specialized area of the Glut determine the postsynaptic response. The number and the proportion between AMPARs and NMDARs, but also their relative position on the PSD, are probably the most important. The number of AMPARs and (partially) of NMDARS is activity-dependent and their relationship and dynamics is the base for the postsynaptic LTP and LTD. The subunits composition of the receptors, which can also vary as a function of the synaptic activity, is another important factor of the postsynaptic modulation of the response. However, the biophysical properties of the spine, and especially those of its neck, play a significant role both in shaping the single synaptic event and influencing the long-lasting effects.

Extrasynaptic information flow control

It is common practice to isolate the synaptic response by blocking all those signals considered as noise to study the single synaptic event. For example, to study the synaptic conductance, the larger part of experiments is performed by blocking the postsynaptic AP activity (for example, by tetrodotoxin). However, this is not the real situation in which the synapse transfer information in the living brain. A typical pyramidal neuron in situ can have a dendritic variation of V_m which are activity-dependent and can be due either to AP backpropagation (among many other Tsay and Yuste 2002; Remme et al. 2009; Schmidt-Hieber et al. 2017) and to dendritic activity produced by the more or less synchronous firing of several synapses (Di Maio et al. 2018b, 2020). The AP backpropagation and the dendritic synaptic activity, either independently or integrating their activity, directly influence the synaptic response because they both modify the value of V_m and then the driving force producing the EPSC (Tsay and Yuste 2002; Di Maio et al. 2018b, 2020).

The dendritic activity is participated both by excitatory and inhibitory GABAergic ($GABA_A$) synapses; the former inducing depolarization and the latter tending to contrast excitation by re-polarizing the membrane. Although the GABAergic synapses in the dendritic tree represent only the 10–20% of the total number, their control of the excitation can be very powerful because of their strategic position on the shaft of dendrites which permit them to be simultaneously on the path of several excitatory synapses. The level of influence of these integrated signals on the response of a specific synapse (**S**) depends on the biophysical properties of the dendritic branch and of the spine of **S**.

Another factor influencing extrasynaptically the information flow by a single synapse is the presence of glial cells (mostly astrocytes, located in the proximity of the synaptic cleft), in the close proximity of the synaptic cleft, which contact both to the pre and postsynaptic side of the Glu synapse.

Dendritic regulation of the single EPSP

From the biophysical point of view, dendrites follow the cable properties (Rall 1962, 1974) and this means that both AP backpropagation and the signals due to the synaptic activity have an influence limited by the distance from the

origin of the signal. However, an active propagation of these signals is possible thanks to active mechanisms which complete the electrical properties of dendrites (Beierlein 2014) and the so-called "dendritic computation" is essentially based on the interaction between their passive and active properties (Häusser 2001; London and Häusser 2005; Rumsey and Abbott 2006; Spruston 2008, 2010)

In this context, it is important to outline that the biophysical passive properties of the dendritic branches, in the same neuron, vary with the distance from the soma (Rall 1974; Magee and Cook 2000; Häusser 2001; Rumsey and Abbott 2006; Beierlein 2014). The dendritic input impedance, for example, being dependent on the size (diameter) of the dendritic branch, increases with the distance from the soma (Rall 1974; Magee and Cook 2000; Häusser 2001; Rumsey and Abbott 2006; Beierlein 2014). An important effect of this is that, for the same EPSC amplitude, a synapse located peripherally produces a higher EPSP than one positioned close to the soma. This property has risen the idea of "dendritic democracy" which assumes that the higher depolarization due to the distance counterbalance the higher influences on the AP activity of the synapses located closer to the soma (Häusser 2001; Grillo et al. 2018). "Synaptic democracy", however, is not only dependent on the biophysical properties as originally assumed because it has been shown that, in several pyramidal neurons, the total synaptic conductance also increases with the distance from the soma contributing to a form of signal equalization among the different synapses of a neuron (Roth and London 2004).

By traveling into the dendritic branches, the integrated signals generated by the different synapses produce strong influential effects on the activity of each synapse (Palmer and Stuart 2009; Di Maio et al. 2018a, b, 2020).

The single bit of information (EPSP) produced by a specific synapse **S** can be variable in amplitude and time course because of the activity of the other synapses (Di Maio et al. 2018b, 2020). The depolarizing wave created by the integration of the activity of the excitatory synapses, for example, reaching the base of the spine of **S**, and depending on the difference of V_m between the dendrite and the PSD, can produce a current which, flowing through the neck, modifies the driving force that generates the EPSC (Di Maio et al. 2018b, 2020, and see Eq. (9)).

To show these effects, we have simulated the synapse **S** with our model used to study the variability of the single synaptic event (Ventriglia and Di Maio 2013a, b; Di Maio et al. 2016a, b, 2018a, b, 2020, and see Sect. 3.2) by including the spine circuit of Fig. 5. The EPSP of each synapse belonging to pools of different sizes (different number of active synapses) on the dendritic tree has been simulated by the difference of two exponentials which is a method often used also to model the field potentials (Sargsyan et al. 2001).

$$V_i(t) = \begin{cases} ak\left(e^{-\left(\frac{t-t0_i}{\tau_2}\right)} - e^{-\left(\frac{t-t0_i}{\tau_1}\right)}\right) & for\, t > t0_i \\ 0 & for\, t \le t0_i \end{cases} \qquad (10)$$

where $V_i(t)$ is the contribution to the potential at the base of the spine of **S** due to the ith event of an active synapse, a defines the synaptic type (excitatory = 1 and inhibitory = −1), k is a factor to adjust the amplitude, $t0_i$ is the activation time of the ith synapse of the pool, τ_1 and τ_2 are the rising and decay time constant, respectively. By changing the values of the parameters of the above equation it is possible to reproduce the attenuation effect of the signals along the dendrites according to the cable properties. In Fig. 6 are shown examples of EPSPs obtained by changing the value of k (panel A), of τ_1 (panel B) and of τ_2 (Panel C).

In a first approach, we used pools, of different size, composed of only excitatory synapses and firing with different mean frequencies (Di Maio et al. 2018b). In a second set of experiments, we used only two pools, of size 100 and 200 synapses respectively, but including inhibitory synapses in the proportion of 20% of the total (Megías et al. 2001; Merchán-Pérez et al. 2014)). Across the different simulations, the parameters of Eq. (10) (k, τ_1 and τ_2) were randomized by appropriate uniform distribution ($U(X_{min}, X_{max})$. The mean excitatory firing frequency ranging 0–6 Hz were combined each with any of the mean inhibitory firing frequencies in the range 0–12 Hz. The specific firing frequency of each synapse was chosen according to a Gaussian distribution ($\bar{\phi}_s = G(\mu, \sigma)$) with $\bar{\phi}_s$ being the mean frequency and σ, chosen such to have a coefficient of variation $CV = \frac{\sigma}{\mu} = 0.5$, was the standard deviation. The precise times of firing ($t0_i$ of Eq. (10)) for each synapse were obtained by a Poisson distribution

$$t0_{i_j} = t0_{i_{j-1}} + P\left(\frac{1}{\phi_i}\right), \quad \forall \quad t0_{i_{j-1}} < T \qquad (11)$$

with $t0_{i_j}$ being the starting time of the jth event of the ith synapse and T is the total simulation time. With such a procedure and mediating over 1000 runs we have got a robust mean representation of the synaptic activity occurring in the proximity of the synapse **S** (Di Maio et al. 2018b, 2020).

To outline the contribution of dendritic synaptic integration on the response of the single synapse, in our simulations we excluded the effect of the AP backpropagation and, therefore, the contribution of the whole pool to V_m at the level of the PSD of **S** was

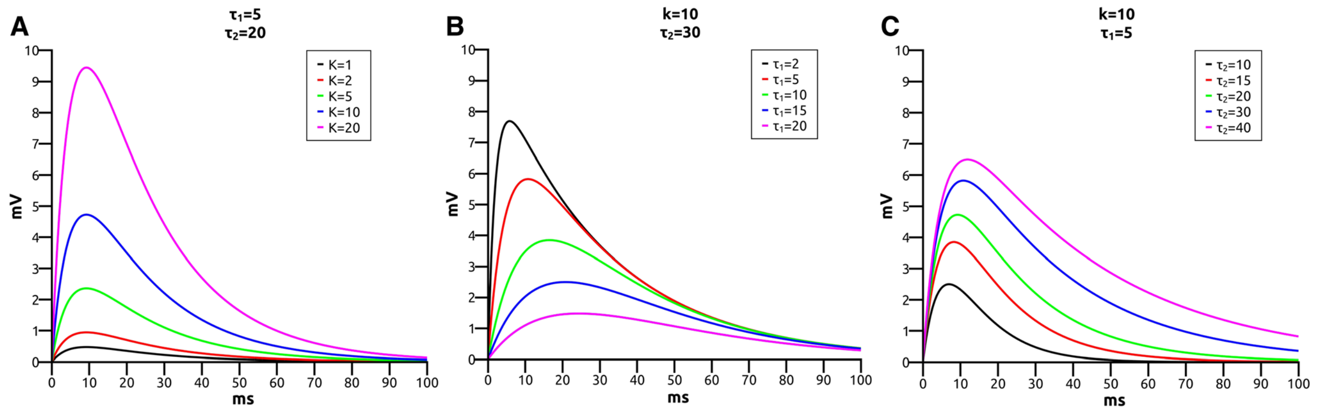

Fig. 6 Variability of the EPSP depending on the parameters of Eq. (10). Panel A: τ_1 and τ_2 are kept constant while k is varied. Panel B: k and τ_2 are kept constant and τ_1 is varied. Panel C: k and τ_1 are kept constant and τ_2 is varied

$$V_d(t) = \sum_{i=1}^{n}\sum_{j=1}^{m} V_{i,j}(t) \tag{12}$$

$$I(t) = G_s(t)(V_m(t) - V_{rev}) + \frac{(V_m(t) - V_d(t))}{R_n} \tag{13}$$

$$V_m(t) = I(t) * R_{PSD}. \tag{14}$$

where $V_d(t)$ is the value of the membrane potential at the base of the spine, $V_{i,j}(t)$ is the contribution of the jth event of the ith synapse belonging to the pool, R_n is the neck resistance and R_{PSD} the input resistance at the level of the PSD.

Our results have shown that both the size of the pool and the mean firing frequencies of the active synapses modulate the amplitude, time to peak, and time course of the EPSP of **S** (Di Maio et al. 2018b, 2020).

The integration of the pool activity produces oscillations of V_m and this oscillation has an amplitude which is a function of the number of the active synapses and on the mean excitatory and inhibitory firing frequencies (Di Maio et al. 2018b, 2020). To be more precise, for any size of the pool and any given combination of mean excitatory and inhibitory firing frequencies, exists a specific amplitude of oscillation (band) the mean value of which can be a good estimator of the specific depolarization level of the band itself (Di Maio et al. 2020).

In Fig. 7 are shown two examples of simulations of Vm at the PSD level considering an EPSP of **S** occurring after $t = 600$ ms from the simulation start ($t_o = 0$), for a pool of 200 synapses (160 excitatory and 40 inhibitory) firing with mean excitatory frequencies of $\bar{\phi}_e = 5 \pm 2.5$ Hz (black line) and $\bar{\phi}_e = 6 \pm 3$ Hz (red line) and a single mean inhibitory frequency of $\bar{\phi}_i = 3 \pm 1.5$ Hz. The left panel shows the results obtained by a single run which should represent the real conditions at which the EPSP occurs in the living brain (Di Maio et al. 2018a, b, 2020). The amplitude and level of the voltage bands for the two different excitatory frequencies can be intuitively identified. The right panel shows V_m mediated over 1000 runs. The difference of the mean value of V_m in the two different conditions shows that the variation of only 1 Hz of the mean excitatory frequency (from 5 to 6 Hz) produces a mean V_m jump of ~ 7 mV which, as for Eq. (9), produces a significant reduction of the amplitude of the EPSP **S** (Di Maio et al. 2020). The results of the left panel of Fig. 7 show also that it is unlikely that, in the living brain, an EPSP starts at the resting level. The starting level (which affects the amplitude of the EPSP) depends on the coincidence of the synaptic event of **S** with the specific dendritic activity.

The above results demonstrated that, in the living brain, the situation is far different from those observed in the experimental conditions and that the single bit of synaptic information depends strongly on the activity of the post-synaptic neuron and on the inputs it receives. Moreover, pushing this argument to its limit, we can say that if the depolarization at the PSD of **S** induced by the dendritic activity reaches the value of the reverse potential (V_{rev} in (9)), then the resulting amplitude of the EPSP of **S** can be $0mV$ and this means that the corresponding presynaptic AP, independently of the vesicle release probability, will not have a corresponding EPSP in the "synaptic code" (Di Maio 2008). By extending this reasoning, we could also argue that the dendritic activity produced by other synapses can veto the transmission of the information carried by the synapse **S** and this could be a competitive mechanism among the synapses for the information to pass to the neuron.

The inhibitory synapses favor the information transfer because the re-polarization they produce drives the V_m far from the value of the reverse potential. Moreover, reducing to 0 pA the EPSC does not imply that the presynaptic neuron cannot transfer any information. A net synaptic

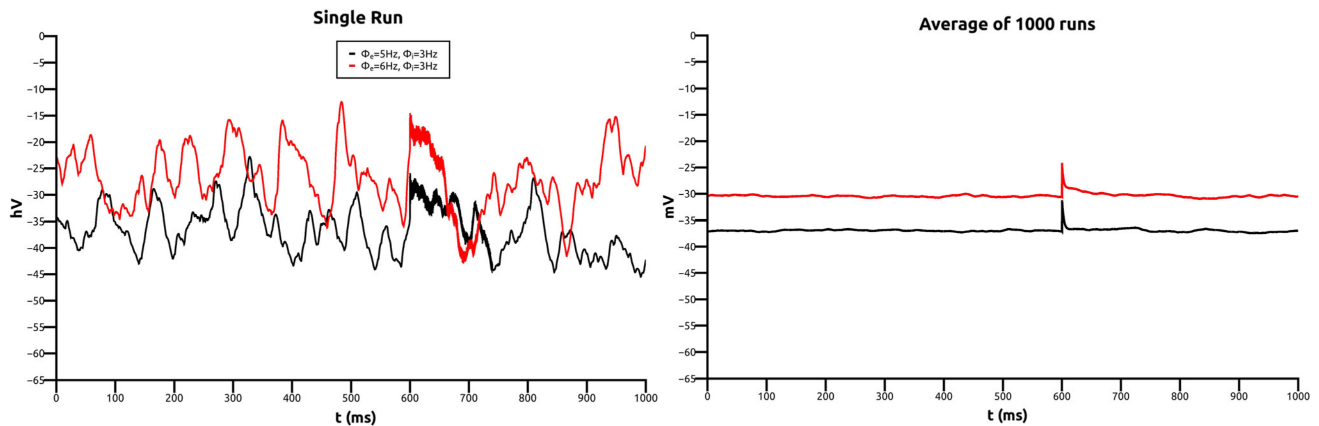

Fig. 7 Left panel: Results of a single run simulation of an EPSP occurring after 600*ms* while a pool of 160 excitatory and 40 inhibitory synapses fires in neighbor dendrites with respectively a mean excitatory frequency of 5 Hz (black line) and 6 Hz red line and an inhibitory firing frequency of 3 Hz. The right panel is the same as the left panel but averaged over 1000 runs

current of 0 pA can still permit the inward flow of Ca^{2+} (counterbalanced for example by a K^+ current) which, entering the NMDARs, can promote synaptic plasticity. However, for $V_m = 0$ mV the probability of NMDARs recruitment is high (see Sect. 5.2).

Dendritic synaptic activity integration mostly depends on two mechanisms, namely the coincidence detection and the temporal integration (Xu et al. 2006; Di Maio 2019; Di Maio and Santillo 2020; Di Maio et al. 2020), which can be independent or coincident with the AP backpropagation, but can contribute also to the synaptic plasticity.

Both the AP backpropagation and dendritic synaptic integration depend on voltage-gated channels present in the dendritic arborization, on their localization, on their number and density (Sabatini and Svoboda 2000; Araya et al. 2007; Rozsa et al. 2004; Reznik et al. 2016). Dependent on the neuron type, the dendritic voltage gated Na^+-channels can be either uniformly or non uniformly distributed in the dendritic tree. In the case they are uniformly distributed, as for example in pyramidal neurons of CA1 area of hippocampus, they sustain a uniform spread of AP back propagation (and synaptic integration) into the tree (Magee and Johnston 1995). Alternatively, their non uniform distribution can produce preferential paths for AP back propagation contributing also to the non linear integration of the dedritic activity. In addition, dendrites can have also Ca^{2+} voltage-dependent channels (Tsubokawa et al. 2000; Nakamura et al. 2002; Rozsa et al. 2004; Beierlein 2014) which can be located also on the spines (Koester 1998; Araya et al. 2006; Hu et al. 2018). The activation of these channels amplifies the action of the AP back propagation and of the synaptic integration determining, depending on their topographical distribution, the areas where the depolarization waves can spread in the dendritic tree. In all cases, dendritic integration modulates the single bit of information (EPSP), by modulating V_m and can also conditioning the recruitment of NMDARs contributing to the synaptic plasticity (LTP and LTD).

The role of Astrocytes on information flow

The original idea that astroglial cells have a simple supporting role in the neuronal organization in the brain has been overcome over time and, presently, astrocytes are intensively studied for their important role in synaptic transmission and information processing (for reviews see Hamilton and Attwell 2010; Araque et al. 2014; Savtchenko and Rusakov 2014; Rusakov and Dityatev 2014; Heller and Rusakov 2015; Bazargani 2016; Kittel and Heckmann 2016; Heller and Rusakov 2017). At many Glut synapses, processes protruding from an astrocyte contact simultaneously pre and postsynaptic sides, and this organization is named "tripartite synapse" (Haydon 2001). Tripartite synapses seem to be $\sim 60\%$ of the total in the CA1 area of hippocampus (Sibille et al. 2014). However, the role of astrocytes in the synaptic transmission remains very controversial although some points are largely accepted. They are known to be active in recovering Glu after release contributing to its clearance from the cleft utilizing electrogenic Na-dependent glutamate transporters (López-Bayghen and Ortega 2011). Glu spilled out the synaptic cleft also bind to astrocytes receptors producing a transient Ca^{2+} current, partially due to an inward flow current and partially released from the internal reticulum, which can produce an excitation wave (Dani et al. 1992; Zur Nieden and Deitmer 2005). The Ca^{2+}-dependent depolarization can produce the release of gliotransmitters and Glu, which influence the transmission of information by acting both on presynaptic metabotropic receptors and postsynaptic receptors (Wade et al. 2011). Interestingly,

one astrocyte can cover several synapses simultaneously and the calcium wave can travel among different astrocytes probably through gap junctions (Dani et al. 1992; Zur Nieden and Deitmer 2005; Wade et al. 2011). The release of Glu by astrocytes can influence the probability of release at the presynaptic side but also the postsynaptic response. However, the ability of astrocytes to contact several synapses, probably forming a sort of information transfer center, is an extremely intriguing factor in the study of synaptic information control. It is not in the scope of the present review to detail the role of astrocytes in the tripartite synapse. The important point is that they represent a controversial additional system of regulation of the information transfer the role of which will need a big effort to be fully unveiled.

Summary of extrasynaptic control

By considering as extrasynaptic all that is external to the spine, a very important role in modulating the synaptic response is played by extrasynaptic factors. The location of a synapse in the dendritic tree is the main factor. The biophysical, passive and active, properties of the dendrite and, consequently, the possibility that other signals, including synaptic activity and spike backpropagation, can affect the synapse output, depend on the position of the synapse on a particular area of the dendrites.

Excluding the astrocytes, all the other factors modulate the synaptic response by acting on the level of membrane depolarization. Astrocytes, instead, seem to have a wide range of activity since they can act simultaneously at the pre and postsynaptic side as well as their potential ability to communicate information among different synapses.

Discussion

The present review has been devoted to illustrating, although partially, how finely tuned the information flowing among neurons in the brain is. A separation of the mechanisms of information control in pre, post and, extrasynaptic is proposed merely for convenience since, with complex interactions, all of them are interconnected contributing synergistically both in modulating the single bit of information, the "neuronal code" transfer, and the rising of cognitive processes involved in memory formation, reasoning, and learning.

At the presynaptic side, the information flow control regulates both single quantum and the sequence of quanta release following a sequence of APs. The single quantum of information (single EPSP) is modulated by the position and quantum content of the released vesicle. This form of regulation is possible because the vesicle diameter and the Glu concentration vary among vesicles and for the different mechanisms used for the release ("full fusion" or "kiss and run"). In this respect, it remains to be clarified which one of these causes of variability depends on stochastic processes or if, in some way, the position and content of the released vesicle depend on the type of information to transfer.

The control on the formation of the "synaptic code" formed in response to the presynaptic "neuronal code" (i.e., the correspondence between the sequence of presynaptic AP and the EPSPs generated) depends on the probability of release of a quantum in response to a single AP. The number of vesicles in the different pools, their mobility among the pools, the number of the docked vesicles, the type, and properties of the SNAREs complexes, the number, density, position, and distance of the VGCC to the vesicles, are all factors influencing the release probability and, consequently, the degree of correspondence between the APs sequence ("neuronal code") and the EPSPs sequence ("synaptic code"). In summary, the presynaptic neuron has both mechanisms shaping the postsynaptic response and determining the structure of the "synaptic code". Both these mechanisms, with their variability activity-dependent, concur to LTP and LTD formation.

Once a quantum of Glu has been released, depending on the parameters considered above, a specific time-dependent concentration profile is produced into the cleft. The structures of the cleft have their weight in shaping the synaptic response.

The synaptic response is produced by the receptors on the postsynaptic side. AMPA and NMDA receptors, with their different role and different dynamics, shape the single EPSP determining its amplitude and time course. Two main factors concur in shaping the EPSP and forming the synaptic plasticity (LTP and LTD): their tetrameric composition and the number.

Postsynaptically additional factors of EPSP modulation are the biophysical properties of the spine. The high input resistance at the level of the PSD can produce, even for a small current (for example produced by the fast AMPA response), a variation of the depolarization level capable of inducing the partial recruitment of the NMDA receptors but, very likely, can also activate VGCC in the neck of the spine modifying the driving force which determines the amplitude of the EPSP. Moreover, the neck of the spine can be subject to transient modifications of its resistance due to small variations of its diameter following the Ca^{2+} current which implies a local variation of the osmotic pressure. This effect can both induce modification of the driving force at the PSD, modulating the EPSC amplitude, and

determine the amount of information flowing through the neck from the synapse to the dendrite and the soma.

Almost all the postsynaptic control systems of the single synaptic event are based on the tuning of the driving force which produces the EPSC. Alternatively, processes due to repetition of EPSPs, dependent on the input frequency (LTP or LTD), act mainly by modifying the number of receptors.

Extrasynaptically, the first important role of astrocytes is to recover Glu which, through complicated passages, will be given back to the presynaptic neurons. The availability of Glu at the presynaptic neuron influences the pool's formation and distribution and, consequently, the probability of release of the vesicles (see above Sect. 4.2). But this is not the only role of astrocytes. They can also release Glu if a Ca^{2+} dependent excitation wave is produced. The double role of recovering and release of Glu can modulate directly the concentration time course in the cleft on which depends the shaping of the postsynaptic response.

The role of astrocytes in the "tripartite synapse", however, is even more complex. A single astrocyte covers simultaneously several synapses and it is also in connection with other astrocytes. The Ca^{2+} dependent wave of excitation produced by Glu sensitive ionic receptors can travel along all the astrocyte membrane and to other connected astrocytes through gap-junctions. It is arguable, therefore, that the role of astrocytes in tripartite synapses could be much more complex than supposed up to now. They could operate, for example, as a sort of "information centers" which inform each synapse in a given area of the levels of activity of the other synapses. We can say that the complexity of the roles played by astrocytes in modulating the single event and possibly the EPSP sequence of the "synaptic code" is very complex and far from being elucidated.

The total dendritic activity, including the spike back propagation, plays such an important role in modulating the single synaptic event to be able to tune its amplitude from the maximal possible value (according to the specific synaptic conductance) up to the 0 mV (in the case $V_m = V_{rev}$). The level of modulation depends on the position of the synapse on the dendritic tree because to a given position corresponds specific biophysical properties of the dendritic branch and a specific distribution of the voltage-dependent ionic channels.

Conclusions

The goal of the present review has been to outline the complexity of the regulatory processes involved in the synaptic information flow from the pre- to the postsynaptic neuron. These processes are governed by several complex mechanisms which, at the present stage, are far from being all fully understood either singularly and in their reciprocal interactions.

Many of the control mechanisms, both at the pre and postsynaptic sides, are still a matter of debate, and different opinions face their real functionality.

The concluding remarks are, then, necessarily restricted to some points and considerations intended to outline the unresolved problems which are open challenges for future neuroscience.

1. The flow of information among Glut synapses is not a simple input/output relationship among two different neurons. Both the transfer of a single elementary bit of information or a "word" coded by a sequence of elementary bits depends not only on the states of the pre and postsynaptic neurons but also on external factors.
2. The "neural code" of the presynaptic neuron is not simply translated into a "synaptic code" but undergoes a sort of rearrangement which is activity-dependent. An increased presynaptic activity increases the probability that a quantum is released following a presynaptic AP (referred to as presynaptic facilitation). The increased of quanta released induces LTP by strengthening the synaptic response, but, in parallel, optimize the "synaptic code" approximating better the APs sequence.
3. The information transferred can be directly modulated by the postsynaptic neuron. While each synapse inputting on a neuron participates in the formation of the postsynaptic "neuronal code" (postsynaptic APs sequence), the backpropagation of the AP modulates the amplitude of each synaptic input acting directly on the driving force which produces every single EPSC when the AP backpropagation is coincident with the synaptic activity. The level of influence of the AP backpropagation on every single synapse, however, depends on the position of the synapse on the dendritic tree and the local distribution of voltage-gated channels. In short, this is a mechanism by which the postsynaptic neuron modulates the input it receives.
4. Synapses talk to each other. Depending on the distance, the cable properties of the dendrites, and the presence of voltage-gated channels, the signal of each synapse spreads in an area where it meets and integrates the signals produced by other synapses. The integration of all the active synaptic signals, not only determines the postsynaptic spiking activity, but also induces local dendritic variations of V_m which modulate the input arriving from any single synapse. This variation of V_m

is modulated by the concurrent activity of excitatory and inhibitory synapses and on their relative distance.

5. By joining the point 3. and 4., we can say that the dendritic synaptic activity and the postsynaptic spiking activity, integrating their action in the appropriate time window, participates to the modulation of the information transfer by every single synapse.
6. External elements like astrocytes, thanks to their simultaneous relationship both with pre and postsynaptic neuron, influence significantly the synaptic response but also produce an effect of sharing information among the different synapses with which they can simultaneously be in contact.

Few additional remarks can be outlined.

While the “neuronal code” is essentially modulated by the frequency of APs or by their precise sequence, the “synaptic code” is also modulated in the frequency but, the single bit of information is modulated in amplitude and, consequently, it is arguable that the “synaptic code” is modulated both in frequency and amplitude. This dual method of coding makes it even more difficult to decrypt the “synaptic code” than the “neural code”. In this respect, an important question arises: *what is the meaning of the amplitude modulation of the single bit in terms of information?* The answer to this question is an important challenge because this modulation has a directly impact the generation of the postsynaptic “neuronal code”, on the modulation of dendritic synaptic activity, and on LTP and LTD generation on which memory and learning are based. About the transfer of the code from the pre to the postsynaptic neuron, an additional outline is related to the modification, activity-dependent, of the probability of release of quantum following a presynaptic AP. This aspect allows us to propose that the presynaptic increasing in quantum release probability optimizes the code transfer because increasing the number of EPSPs in the “synaptic code” increases the level of mirroring between the “neuronal code” and the “synaptic code”. In simple (metaphorical) words: *by an appropriate presynaptic activity the presynaptic neuron “learns” how to transfer the code to the postsynaptic neuron*. This effect occurs in parallel with the formation of the presynaptic LTP which consists in a reinforcement of the synaptic response and, if the above statement can be accepted, we could argue that the base for learning and memory stays essentially in the concurrent realization of the increased synaptic strength and the improved reliability in the synaptic code transfer. The above aspects and conclusions can be considered as questions that neuroscience needs to answer if the goal of understanding information processing in the brain is to be pursued.

In this respect, it has to be considered that, to have a complete sight on the transfer of information among two neurons, a very large amount of parameters has to be taken into account. This is true both if we want to consider the transfer of every single bit of information or the whole code.

The unveiling of all mechanisms which regulate the information processing in the brain is of great interest for developing plausible models related to the single neuron, neural networks, information processing, brain computational ability, and also for the application of biologically plausible neural networks in AI and other practical applications in robotics. For this reason, the study of these mechanisms of control of the information flow among synapses will be among the most important challenges of the future neuroscience and to overcome these challenges will require multidisciplinary approaches with the cooperation of experimental and computational/modeling scientists supportted by technological advances in all disciplines.

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