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Chapter

Information Processing and Synaptic Transmission

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Abstract

The brain is probably the most complex machinery for information processing we can imagine. The amount of data it manages is extremely huge. Any conscious or unconscious event both internal and coming from the environment needs to be perceived, elaborated, and responded with an appropriate action. Moreover, the high-level activities of mind require the connection of logical elaboration, the relationship with past experience (memory), and the transfer of information among different areas of the brain participating to the elaboration of the thought. Almost all brain illnesses or even simple defaults can be related to a corruption of the basic system which manage information in the brain. The main actors in transferring and managing information are the synapses, and then the understanding of the brain information processing cannot disregard the full understanding of the synaptic functionality. In the present chapter, by using as example the most common type of the brain synapse (the glutamatergic synapse), we will present the basic mechanism of synaptic transmission stressing some of the most relevant mechanisms which regulate the transfer and management of information.

Keywords: information processing, synaptic transmission, synaptic integration, neuronal spikes, neuronal modeling, synaptic modeling

1. Introduction

The brain is probably the most complex computational machinery performing in parallel a continuous elaboration of information coming from the environment and from the internal of the body. Undoubtedly, independently from the level of investigation (from the molecular to the neurological and psychological level), almost all the neurosciences deal, directly or indirectly, with the brain information processing and/or its malfunctioning. In this chapter, we will illustrate some basic aspects of information transfer and elaboration showing how much complex is the control of its flow among the neurons.

Neurons share information mainly by the synaptic contacts which they use both to transmit and to receive. The input and output contact among many neurons are the system which operate the neural networks and the whole brain. Synapses are, then, the key points for the information transfer among neurons, but, as we will see in details later, they are also the primarily system of information coding and elaboration. Their activity, in fact, produces the codification of the information by a neuron in form of spike sequences into a sequence of postsynaptic potentials (PSP) which we can define as the first step of the postsynaptic representation of the
presynaptic code. If we consider the spike sequence of a presynaptic neuron as the representation of a stimulus, the PSPs produced at the synaptic level will be the synaptic representation of that stimulus. The meaning of stimulus, however, does not only refer to the codification of an environmental stimulation. The spike sequences, in several neurons, are not only the codification of stimuli but participate also to the high-level performances connected to memory recall, thought, reasoning, and so on. Whatever is the role of the spike sequence, it represents an information which, transmitted to other neurons, is translated at the synaptic level in a sequence of PSP. How this will be further recoded into a postsynaptic spike sequence depends on a complex integration of all the inputs arriving to the neuron in a compatible time window.

Although a large effort is spent in the last five decades for its understanding, the way the neurons really code, manipulate, and share information remains a mystery. What seems to be generally accepted is that the code of a neuron, for a given event, is formed by a sequence of elementary bits (spikes) in a given time window. The difficulty in understanding the code for a given stimulus rises because this sequence often seems to be randomly distributed in time (irregular and non-repetitive interspike intervals) also when generated for the same stimulus. So far, two main ideas have been affirmed on the possible nature of the code, and both of them are supported by many strong experimental evidences. According to one of them, the codification of the stimulus occurs in terms of frequency of the spikes in a given time window. Many different time sequences of the spikes can give the same frequency since it depends on the number of spikes given in the chosen time window. The alternative one assumes that the coding is embedded in the precise timing of the spike occurrence.

The difficulty in understanding the relationship between the code generated by neurons in sequences of spikes (either as frequency or precise timing) rises essentially by the lack of the precise knowledge on how the neuron generates spikes thanks to the thousands of synaptic inputs it receives. In turn, this lack of knowledge depends on the still low level of knowledge on how the synapses code the presynaptic information into a sequence of PSP. The understanding of the basic mechanisms of synaptic transmission is fundamental in all fields of neurosciences including the genesis of important brain diseases involving memory impairment and other brain performances as Parkinson [1], Alzheimer [2], and Autism [3]. Not surprisingly then a big effort is spent nowadays worldwide to study synaptic transmission with the most diverse experimental approaches but also with mathematical modeling and computer simulations since, for the structural conformation, not all the properties of the synapses can be unveiled by the experimental approaches.

In the present chapter, we will use the most common type of excitatory synapse in the brain, the glutamatergic synapse, to outline, after a brief simple explanation of its functioning, how many and how complex are the mechanisms controlling the flow of information among the neurons operated by these synapses.

A typical pyramidal neuron of the cortex or of the hippocampus subfields receives thousands of synaptic inputs (3000–30,000) [4–6]. The larger parts of these inputs (80%) are excitatory inputs which use glutamate (Glu) as neurotransmitter. It is then reasonable to assume that these synapses are the most important way of information transfer and elaboration. Probably, the most important regulatory system of the activity of the glutamatergic pyramidal neurons is given by the inhibitory neurons which use the γ-aminobutyric acid (GABA) as neurotransmitter [4–6].

GABAergic synapses represent between 10 and 20% of the synapses inputting on a pyramidal neuron, and they are located in strategic positions on the shaft of the dendritic branches among the excitatory glutamatergic synapses [4–6]. Glutamatergic synapses are normally located on spines (a sort of elongation)
protruding from the shaft of the dendritic branches. When activated they produce
the so-called excitatory postsynaptic current (EPSC) which is a current which
depolarizes the membrane (increases $V_m$) producing the so-called excitatory post-
synaptic potential (EPSP). The regulatory effect of the GABAergic (mainly GABA_A
type) synapses is to repolarize $V_m$ by the so-called inhibitory postsynaptic current
(IPSC) producing the opposite effect on the membrane voltage and generating the
inhibitory postsynaptic potential (IPSP).

The integration of the activity of these large amounts of inputs at the soma of the
neuron determines the spiking behavior of the neuron (coding). Considering that
on the average a neuron makes a single synapse to another neuron, each neuron
receives contacts from thousands of neurons each of which try to send the infor-
mation it carries. However, several neurons of a given area (sending area) can give
each a single contact to the same neuron (receiving neuron). If the many neurons of
the sending areas are excited by a stimulus, the integration of the synaptic responses
on the receiving neuron will produce the postsynaptic representation of the stimu-
lus. For example, several neurons of the dentate gyrus can input on the same neuron
of one of the subfields of hippocampus (CA1 or CA3) [7]. Moreover, such an input
interacts with the inputs coming from other neurons located on different areas
e.g., from the entorhinal cortex in the example given before [7]).

If we only look to this short and incomplete representation of the problem of the
information management by a single neuron, it becomes clear how and why the
 correspondence between the sequence of spikes and the code it generates is very
variable such that the correlation between the inputs and the code generated is
unpredictable and appears random.

In this framework, a great amount of complexity depends on the mechanisms
which regulate the transmission of a single bit (spike) information to each synapse.
The synaptic activity is greatly influenced by many factors [8]. First of all, the way
glutamatergic synapse contributes to the postsynaptic neuronal code depends
strongly on the biophysical properties of the dendrite where the synapse is located
and on the path from its location to the soma. The electrical signal generated at a
synapse attenuates with distance according to the cable properties of the dendritic
path which changes along the arborization depending mainly on the dendritic size
[9, 10]. The attenuation with distance is of exponential type [9, 10]. Usually, the
higher input impedance of the branches more far from the soma seems to help the
diffusion of the far signals producing EPSP with higher amplitude, a phenomenon
which some authors consider as a sort of “synaptic democracy” [11, 12].

To give an idea of some of the basic mechanisms involved in the modulation of
the synaptic information transferred to a neuron, in the following we will briefly
remember, in a simplified way, the basic mechanism of the synaptic transmission
with a particular attention to those processes which participate to the modulation of
the signal. A part of the ability to transmit and modulate the information depends
directly on the synaptic structure. For this reason we will first describe a general
glutamatergic synapses and after the pre- and postsynaptic mechanisms influencing
the modulation of the information carried by a single bit of synaptic information
(the EPSP). The modulatory effect on a sequence of elementary bits (a “word”) will
also be considered, and a final discussion will summarize the effects of the different
modulatory systems.

2. Synaptic structure and mechanisms

A classical glutamatergic synapse is located on the top of a spine of the dendritic
tree. The spine is composed of a neck, protruding from the dendritic shaft, and a
head where the information is really received. A general description of the glutamatergic synapse includes a presynaptic button facing through a cleft with postsynaptic spine. The area of the presynaptic button, opposed to the postsynaptic spine, contains vesicles filled of glutamate and is called the active zone (AZ). A number of vesicle ranging 10–20 are anchored to the presynaptic membrane by the SNARE complex (soluble NSF attachment proteins) which is a protein complex docking the vesicles ready to be released [13]. The arrival of a presynaptic spike activates the fusion and the pore formation of a vesicle activated by the SNARE complex following the Ca\(^{2+}\) influx (see, e.g., [13]). The first step of the transfer of the single elementary bit of information is then the release of a vesicle of glutamate regulated by the SNARE complex following the arrival of a presynaptic spike. If we consider the spike as the elementary bit of the neuronal information carried, then we can consider the EPSP as the elementary bit of the synaptically coded information.

The presynaptic surface, containing the docked vesicles, is separated from the postsynaptic one by a distance (cleft) of \(~20 \text{ nm}\). The synaptic cleft is a volume where the molecules of glutamate, released by the presynaptic vesicle, diffuse by Brownian motion [14]. The arrival of the presynaptic spike, thanks to the Ca\(^{2+}\) and the SNARE complex, induces the formation of a pore between a vesicle and the presynaptic membrane. This pore is the path followed by the glutamate molecules to transit from the vesicle to the synaptic cleft.

If we assume a generic horizontal section, the diameter of a cortical or hippocampal glutamatergic synapse ranges \(0.2–1 \mu\text{m}\) [15–18]. Assuming an AZ of circular space and the cleft of \(~20 \text{ nm}\), we get a volume of cylindrical space which many authors use to study the synaptic transmission by a computer modeling approach [14, 16, 19]. Not all the synaptic “cylinder” is free for the diffusion of glutamate. The AZ covers only a part of the whole synapse (mean radius 0.11 \(\mu\text{m}\)), while the surrounding part is occupied by fibrils which anchor the pre- and postsynaptic neuron [20–22].

At the postsynaptic side, two types of glutamate receptors are colocalized in an area which is almost of the same size of the AZ and is considered as of circular shape too (lower part of the cylinder) [22, 23]. This area is called postsynaptic density (PSD) and contains \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid sensitive receptors (AMPA receptors) and N-methyl-d-aspartate sensitive receptors (NMDA receptors) which contains sites to bind glutamate molecules (but also for the glycine which is necessary for the synaptic activity). These two types of receptors have different roles in the transfer of synaptic information which we will discuss later in details. Both types are tetramers composed of a dimer of dimers [24]. As we will see later, the dimeric composition of the receptor plays an important role in shaping the postsynaptic response.

Apparently, the information transfer process is very simple in principle. The arrival of a presynaptic spike produces the fusion of a vesicle with the release of glutamate which activate postsynaptic receptors producing a depolarizing current (EPSC) which causes a variation of the postsynaptic membrane potential called EPSP which, diffusing through the dendritic branches, contribute at the soma, to the generation of the postsynaptic spike. However, any of the passage from the presynaptic to the postsynaptic side undergoes to a series of rearrangement of the information which makes the whole process extremely complex both to study and to interpret. In Figure 1 a schematic representation of the information flow by synaptic transmission is presented.

Essentially, the different modulation systems produce a sort of complex nonlinear variability of the postsynaptic response. Variability of the EPSP is caused
both by pre- and postsynaptic mechanisms of control, and a part of this variability seems to be of stochastic nature (for a review see [8]). In the following we will examine some (but not all) regulatory mechanisms which imply modulation of variability of the postsynaptic response and their possible stochastic and/or deterministic nature. Some of the processes which produce synaptic response variability are external to the synapse and will be considered in an appropriate section.

2.1 Intrasynaptic factors of the EPSP variability

For intrasynaptic factors we mean those mechanisms operating at the level of the AZ or to the PSD area. For extrasynaptic we mean any influencer located or operating out of the synaptic “cylinder.” Intrasynaptic factor can be divided into pre- and postsynaptic factors influencing the EPSP variability.

2.1.1 Presynaptic-dependent EPSP variability

A first point to stress about the presynaptic source of variability is that the probability of release of a vesicle following a presynaptic spike is not 1 and the range
can be as wide as 0.2–0.91 [25, 26]. Modification of the releasing probability has been associated to the so-called presynaptic (non NMDA-dependent) long-term potentiation (LTP) assuming that the efficacy activity dependent of a synapse depends on the increase of the releasing probability [17, 27–29]. This point is crucial for the understanding on how the presynaptic neural code is coded synaptically because it means that not all the presynaptic spikes are coded by an EPSP. Moreover, if this probability changes as a function of the activity, this means that a different number of EPSP code for a given number of presynaptic spikes depending on the preceding activity. In terms of information, not all the presynaptic bits are transferred but only a fraction of it, and the size of the fraction is activity dependent. Moreover, the sequence of EPSPs does not sum linearly at the postsynaptic side [30, 31]. This means not only that only a part of bits composing the presynaptic “word” is transferred but also that their postsynaptic representation is extremely variable and depending on how many bits are transferred (which change as the probability of release changes with activity) and on the timing between the transferred bits.

Although the vesicular release is considered of quantal type, the release of single vesicle can produce different responses depending on several presynaptic factors (see, [2]). An important factor is the position of the vesicle (eccentricity) with respect to the central axis of the cylinder limited by the AZ and PSD. For a given configuration of the PSD (see next section), the release of glutamate from a more peripheral vesicle will produce an EPSC with smaller amplitude than one centered to AZ-PSD central axis [32–34]. Another important factor is the amount of molecules into the vesicle. Vesicle concentration, in fact, is extremely variable ranging 60–210 mM [15, 16, 35] with an average of ~140 mM. Assuming an internal radius of the vesicle with an average of 23 nm, it is clear that the number of molecules of glutamate released for a single bit of information is extremely variable. A variable number of molecules produce EPSC with different amplitude [32–34, 36–38]. In our early work on single glutamatergic response, we have considered the combination of the number of molecules and the position of release as stochastic factors [8, 32–34]. However, by considering the large variability of the concentration of glutamate in the vesicles, the thousand possible combinations of “position-number of molecules,” this could be a powerful system of presynaptic regulation of the information transfer. In this respect, an interesting question arise: “what is the mechanism which, for a given presynaptic spike, decide the correct combination ‘position-number of Glutamate molecules’?” The SNARE complex, because of its different configurations depending on the membrane activity, could be a candidate for this decision role [13, 39, 40].

Although in the larger part of the cases a single vesicle opens with probability less than 1 for the arrival of a single presynaptic spike, in some cases a multivesicular release has been observed (see, e.g., [41, 42]). The multivesicular release found in some experiments opens many other interesting questions. The most relevant is: what is the relationship on the number of vesicle opened for a spike the of information transferred? Another interesting question is What is the role of multivesicle release if usually a single release does not achieve postsynaptic saturation of the response? [35, 43]. To summarize, the most important presynaptic factor of EPSP variability are:

- Probability of release of a vesicle following a single presynaptic spike and its dependence on the past activity
- Probability of multivesicular release
- Number of molecules inside the released vesicle
• Position (eccentricity) of the released vesicle

• $\text{Ca}^{2+}$ different modulations of the SNARE complex

2.1.2 Postsynaptic-dependent EPSP variability

The PSD is the postsynaptic area containing the receptors (AMPA and NMDA) with different roles [44]. The number of receptors among different synapses is highly variable but varies also in the same synapse as a function of its maturity and activity. The number of AMPA receptors in a typical hippocampal synapse can range between 0 (AMPA-silent synapses [45]) and 80–100 [46, 47]. The number of AMPA is related to the synaptic maturation and potentiation and is strongly associated to phenomena like memory formation and learning (among many others [17, 29, 48–51]). Some of these mechanisms can change the properties of a synapse in the time-lapse of less than a second if the presynaptic neuron furnishes an appropriate stimulation. The variability of the number of AMPA not only produces potentiation of a synapse but also a de potentiation (by removing of AMPA [52]), and both mechanisms are $\text{Ca}^{2+}$ and NMDA dependent [53]. AMPA can either be inserted (or removed) because a migration from the extrasynaptic membrane space to the PSD or just acquired from the cytoplasm [52]. According to some authors, also the number of NMDA receptors can change as a function of the activity [54]. This point is not trivial for the understanding of the synaptic response variability. By changing the number of receptors, it changes the total conductance and the current that the synapse can produce for a single presynaptic spike (see Figure 2).

Both AMPA and NMDA are tetramers (composed of four subunits) arranged as dimer of dimers. The dimeric and tetrameric composition produces a mosaic of configurations each with electrophysiological properties different from the others [24, 55–60]. Their conductances mediated over different dimeric compositions (as computed in Di Maio et al. Table 2 of [61]), in fact, are for AMPA $15 \pm 10$ pS and for NMDA $40 \pm 15$ pS. This means that the variability induced by the insertion activity-dependent of an AMPA, for example, will furnish a variation of the response depending on the dimeric composition (conductance) of the newly inserted receptor.

The current produced by the opening of the receptors (EPSC) produces a variation of the membrane potential (EPSP) at the postsynaptic side which depends on the biophysical properties of the postsynaptic membrane. The glutamatergic neuron

Figure 2.
Different synaptic responses obtained for the release of a single vesicle. The different amplitudes can be due either for presynaptic regulation (e.g., different positions of the vesicle or different numbers of molecules) or for postsynaptic regulation (e.g., different numbers of receptors or different membrane voltage at the moment of the EPSP start).
synapse is positioned at the top of a spine which is considered by many authors as a separate electrical compartment with a high input impedance [61–67]. The general equation which produces the EPSC is derived by Ohm’s law:

\[ I_{syn}(t) = g_{syn}(t) (V_m(t) - E_{syn}) \]  

where \( I_{syn} \) is the current (EPSC) produced by AMPA and NMDA receptors, \( g_{syn} \) is the synaptic conductance, \( V_m \) is the membrane potential, and \( E_{syn} \) is the equilibrium potential computed by the Nernst equation considering all the ions (usually Na\(^+\), K\(^+\), and Ca\(^{2+}\)) involved in the synaptic current. The values of EPSP expressed as a variation of \( V_m \) depend on the input resistance (\( R_i \)) of the system:

\[ V_m = I_{syn} R_i \]  

As clear from Ohm’s law, for a given current produced by the receptors, the variation of the membrane voltage amplitude depends on the value of \( R_i \). The spine in general is considered as a system with high input impedance (order of GΩ) [9, 10]. However, more recent papers have stressed that the spine circuit is rather complex and can be sub-compartmentalized [46, 62, 63, 67, 68]. However, two main parts of the spine compartmentalization play really a relevant role in shaping the postsynaptic response: the PSD area and the neck resistance [65, 66]. The neck resistance is the natural pathway for the signal to reach first the dendrite and then the soma and will be treated in the next section. About the PSD area, it is the area where the receptors are localized, and its characteristics directly influence the response of each single receptor. Being crowded of proteins, the resistive component of this is high, while the capacitive one is negligible [61, 64–66]. According to Eqs. (1) and (2), the current in this area can produce high variation of potential even for very small currents produced by the receptors (see the dependence of the EPSC and EPSP in Figure 3 of [61]). PSD input resistance then is a key player in modulating the receptor current.

This is even more important if we consider the characteristics of the NMDA receptors and their contribution to the EPSC generation. At the resting level of the membrane potential (\( V_r \sim -65 \) mV), these receptors are blocked by Mg\(^{2+}\), and, consequently, even if glutamate is release, they do not furnish a contribution to the EPSC. Mg\(^{2+}\)-block of NMDA is voltage dependent [55, 69]. The probability of NMDA receptor to give a contribution to the total conductance follows a sigmoid rule function depending on the membrane voltage. The complete unblocking of the total NMDA conductance (unblocking probability = 1) is obtained only for a very depolarized value of \( V_m \) (\( V_m \sim +40 \) mV) which is not a value in the usual range of action of the dendritic synapses [55, 61, 64–66, 69]. However, as we have shown in our recent works [61, 64] because of the PSD high input impedance, the current produced by the fast AMPA receptor activation can increase their probability to unblock and to contribute to the total synaptic conductance. It follows that different number and proportion of AMPA and NMDA produces different effects on the single EPSPs. This is an example of intrasynaptic receptor-dependent modulation of the EPSP which can be considered as due to the receptors’ cooperativity [61].

The influence of the NMDA component on the total EPSP, being voltage dependent, does not only depends on the fast AMPA activation but also on external factors (see the following sections). In summary we can say that the postsynaptic processes involved in the variability of the EPSP are:

- The total number of postsynaptic receptors
- The relative number of postsynaptic receptors (AMPA versus NMDA)
The diversity of the receptor conductance depending on the dimeric composition

The biophysical properties of the PSD

2.2 Extrasynaptic factors of the EPSP variability

By looking just outside the restricted synaptic space, several other factors can influence the EPSP formation. In short we can say that, according to Eqs. (1) and (2), any factor which can influence the membrane potential in the proximity of the synapse can play a role in shaping the EPSP. The first important structure that we found outside of the synaptic space is the neck of the spine. It is the communication way between the synapse and the dendrite, and its electrical resistance determines the amount of information passed to the cell (dendrite). The value of the neck resistance is, then, crucial for the flow of information among different areas of the dendrites and the soma. Spine morphology is variable, and consequently its bio-electric properties [62, 67, 68, 70] and the presence of voltage-gated channels can further influence its ability to transfer the synaptic information [70]. According to some authors, the neck diameter and resistance are modulated also during a single synaptic event [62, 63, 67]. Modulation of the neck resistance produces, as a consequence, a modulation of the EPSP transmitted to the soma. However, the neck does not only carry the synaptic information to the dendrite. It acts also in the opposite direction by carrying the information on the state of dendrite to the PSD. In other words, the PSD is kept informed of the information arriving from other synapses located in the proximity. Dendritic activity, in fact, producing a difference of potential between the dendrite and the head of the spine, produces a net current, the direction of which depends on the difference of potential between the two structures. The current arriving from the dendrite is essentially amplified by the high input impedance of the PSD influencing strongly the total EPSP and the

Figure 3.
Simulation of EPSP during dendritic activity produced by different firing frequencies of excitatory and inhibitory synapses. Depending on the firing frequencies of the other synapses located in the proximity, the membrane voltage under the spine has different amplitude and types of oscillation. The phase and the level of oscillation at the moment of the EPSP start, modulate the amplitude its amplitude and time course. In these simulations the EPSP occurred always at 600 ms. The black line is the time course of the membrane potential if no dendritic activity is present, and hence it is constant at the resting level (−65 mV).
recruitment of the NMDA receptors [65, 66]. The neck of the spine is, then, a powerful modulator of the synaptic information transfer depending on the excitation (depolarization) level of the membrane potential in the dendrites [65, 66].

By considering the huge number of inputs (from $3 \times 10^3$ to $3 \times 10^4$) received, the dendritic arborization is not an electrical isopotential compartment. Differences of potential among the different branches can be due to different input activities and by spike backpropagation [71] in those areas where it can occur. The spike back propagation depends on the presence of Na$^+$ and/or Ca$^{2+}$ voltage-gated channels in the dendrites [12, 63, 70, 72]. The presence and density of these channels differ both among neurons and, in the same neuron, among different dendritic regions [12, 63, 70, 72], and consequently differences of potential can produce complex potential waves transiting the dendrites, and this wave can reach the PSD through the neck resistance influencing the single synaptic event. In our recent papers, we have studied a possible effect of potential waves produced by excitatory synaptic activity on the single synaptic response independently of the spike backpropagation [65, 66]. We have found that, depending on the number of active synapses and on their mean firing frequency, the amplitude, peak level, and time to peak of the response vary in a complex nonlinear fashion (see Figure 3) [65, 66]. The number of active synapses in some way simulates the input, for example, received from one area of the brain where a group of active neurons fire in a more or less synchronous way (in response to a stimulus) on the same neuron in a restricted dendritic area. For the case already mentioned, for example, a neuron of a hippocampal subfield can receive synchronous inputs from a large area (many neurons) of the dentate gyrus but also from areas of the Entorhinal cortex in separate regions of the dendritic branches (see, e.g., [7]). The neurons from one of these two areas fire with a mean frequency and a standard deviation which depends on the degree of their synchronization. Such a condition produces waves into the dendritic area interested to the stimulation which directly influence any single synapse which is active in the same time window [65, 66]. The membrane potential of the receiving neuron oscillates between two levels forming a voltage “band.” The amplitude of this voltage “band” depends on the number of active synapses and on their mean firing frequency [65, 66]. The EPSP of a given synapse can occur at any level inside the “band.” According to Eqs. (1) and (2), depending on the level at which the EPSP of a given synapse starts, its properties (amplitude, peak level, NMDA contribution, etc.) will change [65, 66]. In this band it is possible to identify a mean value which can be considered as the maximal likelihood level of $V_m$ at which the EPSP can occur. This mean level increases (more depolarized) by increasing the number of active synapses and/or their firing frequency [65, 66]. The existence of this “band” of voltage furnish a large gamma of possible levels of $V_m$ at which EPSP can occur and consequently it represents a very powerful regulator of the single EPSP depending on the time of occurrence (phase of the oscillation inside the band) [65, 66]. Said in a different way, the coincidence of the EPSP with the particular level of determines the type and amount of information the synapse transfers. NMDA receptors, being dependent on the membrane voltage for their activity, are especially sensitive to this kind of regulation, and in fact, the “coincidence” of the EPSP with the activity of other synapses is considered crucial for phenomena like LTP and memory which are NMDA dependent. These are the basic mechanisms who suggest that neurons, mostly in producing LTP and memory phenomena, act as coincidence detectors (among many others, see, e.g., [73]). The dendritic activity modulatory effect on the transfer of a single bit of synaptic information depends essentially on the variation of potential in the membrane and can be summarized as due to:
• Spike backpropagation

• Active synaptic inputs on the dendritic tree

3. Discussion

This short overview was aimed to stress how the information transferred among synapses and its elaboration undergo to many regulation systems which involve structural, functional, and cooperative processes. By identifying the EPSP as the elementary bit of the information transferred by a single synapse, we have outlined some of the pre- and postsynaptic sources of variability.

In general the word “variability” can be used with two meanings. It can be attributed either to something which vary in an unpredictable way, or it can mean the possibility to change following specific actions. This is especially true for the causes of variability of the EPSP. EPSP variability can be due (a) to stochastic processes [8, 32–34] or (b) to specific systems of regulation which operate at different levels of the synaptic transmission (intrasynaptic or extrasynaptic). About the stochastic variability, we cannot say too much. If a process occurs randomly, we can only try to understand its effects observing the responses and trying to explain the phenomena by a plausible model which (statistically) describes the natural event. The big problem in this respect is to identify if this type of system depends really on stochastic processes or if stochasticity is apparent because the lack of the full information needed to characterize the processes. From the most top point of view, almost all the causes of EPSP variability described herein can appear of stochastic type [8, 32–34], but we cannot definitively exclude that the apparent stochasticity is due to our incomplete understanding of all the underlying mechanisms and/or to the lack of knowledge of all the steps underlying the process. Just to give an example, if we consider the response variability depending on the number of molecules in the vesicle, its position on the AZ (eccentricity), and its variable release probability, [8, 17, 27–29, 32–34] we can assume a stochastic origin of the presynaptic factors of the synaptic response variability. However, the mechanism of the vesicle opening is under the control of the SNARE complex which is intimately connected to the vesicle and is the responsible for the Ca$^{2+}$ dependent pore opening. This complex can have different configurations depending on the state of the neuron (see, e.g., [13]). We cannot exclude that a more complete understanding of the SNARE complex functionality could permit the definition of a relationship between the information passed by the synapse and the characteristics (position and number of molecules) of the released vesicle. This is only a possibility for one of the many regulatory factors involved in the synaptic response modulation, and their discussion is not in the goal of the present chapter. The important point that we want to stress is to outline the large variability of the EPSP and that this variability is controlled by many different systems. Variability, then, in the context of this chapter, has to be intended as the ability to be modulated (“tuning”) of the system.

The tuning of the information to transfer is not only due to the pre- and postsynaptic neuron. The activity of thousands of synapses inputting on a neuron produces waves of potential into the dendritic tree which directly influence the characteristics of the information transferred by each single synapse [65, 66]. Even two single synapses, closely located on a dendritic branch, influence each other. The synapse which fires first, in fact, by changing the membrane potential influences the response of the synapse firing later if the time interval between the two events is compatible with the decay time of the first event [30].
Two key questions emerge by the above considerations: (a) what is the characteristic of response (EPSP or EPSC) which better represent the code of the single bit of the synaptic information? and (b) how does the single bit of synaptic information produces a synaptic code at the postsynaptic level? The two questions are not independent to each other. The best candidate to code for the single bit of information seems to be the EPSP (or EPSC) “amplitude.” The amplitude depends on the characteristic of the synapse (number of receptors, PSD input impedance, spine neck resistance, etc.) and on the activity of the dendrite on which the synapse is hosted.

The amplitude of an EPSP occurring when the postsynaptic membrane is close to the reverse potential 0 mV can approach 0 mV. This means that the postsynaptic mechanism of tuning can, depending on its state, nullify the information. Alternatively, an EPSP starting when the postsynaptic membrane potential is close to the resting potential (or even in a hyperpolarized state), the amplitude is maximized [65, 66].

Interestingly, if the single bit of information is coded by the EPSP (EPSC) amplitude, while a diffuse excitation depolarizing the membrane reduces the amount of information passed by the synapse, the inhibition works in the opposite direction. Driving the membrane potential far from the reverse potential, in fact, the inhibitory inputs play a favor of increasing the amplitude [30].

Assuming that the single spike represents the single bit of information of a neuron, a sequence of spikes emitted by a presynaptic neuron represent a “word” that is the full representation of a stimulus in that neuron. The synaptic codification of this “word” should be an equivalent sequence of EPSP. This does not always hold. As we have said, the probability that an EPSP is generated when a spike arrives is less than 1. Moreover, EPSPs sum non linearly at the postsynaptic side and the amplitude and shape of the resulting sum depend on the time between the EPSPs. In addition, the different EPSPs are modulated postsynaptically each differently depending on the coincidence of their start and the phase of the wave produced by the dendritic activity. The same presynaptic “word” can then have different postsynaptic representations since formed by different number of EPSPs coded with different amplitudes and presenting different shapes and duration because of the different NMDA contributions. In short, rarely the same repeated stimulus represented by a sequence of spikes will have a fixed clearly identifiable representation at the postsynaptic side. This variability of synaptic representation of a “word” is probably the main cause of the variability of the postsynaptic neuronal “word” (different sequences of the postsynaptic spikes). This means that the single presynaptic “word” almost never determines the postsynaptic spike sequence (postsynaptic “word”) which is always the results of the cooperation of all the inputs arriving in a given time window. Although in many experimental results it is possible to identify a sort of relationship between a stimulus and some characteristics of the spikes sequence it induces in a given neuron, probably in the real brain, the situation is much more complex.

A last comment on how the mechanisms of postsynaptic regulation play a role in the information processing by considering the different information arriving from many neurons on a single one. If we consider the inputs on a single neuron coming from two areas of the brain and located in the close proximity on the dendritic tree, the area which sends early the information can inhibit the information of the other area. A massive input arriving from many excited neurons of a firstly activated area will produce a strong depolarization of the dendritic area which will inhibit (if not nullify) the information arriving from the other area. This can be probably a mechanism which regulates, at the single neuron level, the competition between two antagonist inputs involving different areas of the brain but also a mechanism of “decision-making.” The priority for the response, in this case, is time dependent.
since the single neuron will furnish mostly a response to the area activated early. However, the inhibitory regulation of these mechanisms can produce several different levels of single-neuron response to the two different stimuli. In other words, the mechanisms of regulation of the synaptic information transfer based on the variation of the membrane potential regulate also the competition and/or the level of integration of the information arriving from different areas of the brain on close areas of the dendritic tree of the same neuron.

A last comment on the nature of the codification of the synaptic information and on the computational ability of the dendrites is necessary. While one can discuss on the digital or analogical nature of the neural code which is based on stereotyped spike (bit) sequence, the same does not hold for the transformation of the neural code into the synaptic code at the dendritic level. EPSPs are not stereotyped (all or none) systems, and, as shown before, their representation of the presynaptic “words” change the number of bits, shape, and amplitude. By looking this type of synaptic codification, we would exclude a “dendritic computation” based on algebraic-like or Boolean-type computation (see, e.g., [31]). Most probably, dendritic computation has to be a sort of analog computation which still remains to be understood.

4. Conclusion

In this chapter we have given a non-exhaustive light overview on how the synaptic response is modulated by several intrinsic and extrinsic factors acting at different stages of the process of the information processing and transfer among neurons. A first important point that should emerge from what exposed is that the problem, also at the level of the single synapse, is extremely complicated by the different effects produced by the many systems of modulation of the information.

A second, but not less, important point is that our knowledge of the information transfer by synaptic transmission is still very poor although a great effort is spent in this direction.

The different levels, at which the regulation of the information processing mediated by synapse occurs, require the cooperativeness of different scientific approaches. The experimental methodologies and paradigms of investigations, although improving day by day, cannot answer alone all the questions still open because of the experimental technique limitations. A good synergy between experimental, theoretical, and computational modeling approaches is needed. The possibility to use big computational facility becomes a limiting factor for the success.

The unveiling of the synaptic mechanisms of information processing and transfer is of great importance because information processing is the key ability of the living systems to survive in the environment and, for the humans, is also the key ability for high-level cognitive performance. As stressed in the introduction, the loss of cognitive performance, like in the Alzheimer and in the Parkinson diseases, is strongly associated to the synaptic malfunctioning. Memory and learning are essentially synaptic functions.

In addition, the investigation on synaptic information processing and in the synaptic functionality also support the researches in other fields as, for example, in projecting and realizing artificial computational systems which, by using the powerful mechanism of synaptic information processing, tray to produce high-performance artificial system (see, e.g., [74]).

Some important challenges for the future studies of the information processing mediated by synapses can be summarized as follows:
• Unveiling the presynaptic mechanism involved in vesicle release as function of the presynaptic spike sequence.

• Decoding of the synaptic EPSP sequence as function of the presynaptic spike sequence and its relationship with the presynaptic stimuli which determine the sequence.

• Decoding the real integration systems which relate the information arriving from different areas and their integration at the dendritic level in order to produce the postsynaptic spike sequence.

• Establishing the relationship between the dendritic excitation produced by thousands of synapses and the single synaptic event. This is necessary to understand the real contribution of a single event and of a single presynaptic sequence of spikes in building the postsynaptic EPSP sequence and consequently its participation to the postsynaptic spike sequences (postsynaptic neural code).

All these challenges are very hard, and each of them will need still years of investigation in the field of the information processing in the brain.

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