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Computational modeling of the transfer of electrical signal between neurons, connected through mixed synapses

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Abstract

Synaptic communication between neurons mainly occurs in two different modes of communication - either chemical or electrical. However, the combined evidence from microscopy, immunohistochemistry and electrophysiology experiments confirmed the existence of morphologically mixed synapses, which contains both chemical and electrical synapses. To our knowledge, the putative role of signal transfer through the mixed synapses was not yet addressed in computational neuroscience studies. In this paper, we present data obtained from mathematical and computational modeling experiments. We simulated the transfer of electrical signal between neurons, coupled through a mixed synapse containing an electrical and either an inhibitory (GABA) or excitatory (AMPA or NMDA) chemical synapse. The obtained simulation data revealed that inhibitory effect of GABA synapse is largely obscured by the biphasic response incoming to the postsynaptic neuron from the electrical synapse. In addition, the data showed that some combinations of electrical and an excitatory NMDA (but not APMA) synapses can provide an optimal mixture of conductances to ensure the required firing rates in the postsynaptic neuron. These results may offer at least a partial mechanistic explanation for a relative abundance of mixed synapses containing NMDA synapse, and the rarity of evidence for the existence of other types of mixed synapses.

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Introduction

Brain function requires communication between neurons, which occurs at specialized structures called synapses. Synaptic transmission can be categorized into two basic modes: electrical or chemical. Electrical synapses are formed of gap junction channels, which directly connect two neurons, typically through dendro-dendritic or soma-somatic junctions (Nagy, Pereda, & Rash, 2018). Electrical synapses enables a direct transfer of electrical signal, thus, either a depolarizing or a hyperpolarizing impulse of any amplitude can be transferred through an electrical synapse in a bidirectional fashion. In contrast, transmission through a chemical synapse is one directional and requires that presynaptic neuron would generate an action potential (AP). Depending on its effect on the membrane potential of the postsynaptic neuron, all chemical synapses can be classified as either inhibitory or excitatory (i.e., membrane potential of the postsynaptic neuron is depolarized). That is, an excitatory synapse depolarizes, while an inhibitory synapse hyperpolarizes membrane potential of the postsynaptic neuron after the presynaptic neuron generates an action potential (AP).

Interestingly, both chemical and electrical synapses and coexist in a structure called a mixed synapse. First evidence for existence of mixed synapses were reported in the central nervous systems (CNSs) of birds and lower vertebrates (Bennett, Pappas, Aljure, & Nakajima, 1967; Martin & Pilar, 1963; Robertson, 1963), and the later studies have also identified mixed synapses in mammalian CNS (Korn, Sotelo, & Crepel, 1973). To this day, probably the most comprehensively described mixed synapses are those located between neurons of lower vertebrates, especially at the club endings on the teleost Mauthner cell (Lin & Faber, 1988; A. E. Pereda, Bell, & Faber, 1995; Tuttle, Masuko, & Nakajima, 1986). Even though there are increasing evidence about the occurrence of mixed synapses in mammalian brains, for example, in rodent hippocampus (Hamzei-Sichani *et al.*, 2012) or auditory system (Rubio & Nagy, 2015), mixed synapses are not nearly as prevalent as purely chemical or electrical synapses. Most of the identified mixed synapses contain glutamatergic (i.e., excitatory) NMDA synapses (Bardoni, Magherini, & MacDermott, 1998; Kamasawa *et al.*, 2006; Rash *et al.*, 2005), while the evidence for other types of mixed synapses, for example containing GABAergic (i.e, inhibitory) synapses, thus far are very sparse (Hamzei-Sichani *et al.*, 2012).

To our knowledge, the role of mixed synapses was not yet addressed in computational modeling studies. Thus, to evaluate the putative role of a mixed synapse, we simulated transfer of electrical signal between neurons connected through mixed synapses of different types and conductances. Our simulation data revealed that small inhibitory postsynaptic potentials (IPSPs), transduced to a postsynaptic neuron via an inhibitory GABA synapse, would be eclipsed by a biphasic response incoming from an electrical synapse of a similar conductance. These results might provide a mechanistic explanation for a lack of comprehensive evidence for an existence of mixed synapses containing GABAergic synapses in animal tissues. To evaluate the effect of a mixed synapse on the speed of electrical signal transition, we estimated the delay between APs in neurons coupled through a mixed synapse containing an excitatory (AMPA or NMDA) chemical synapse. The data showed that an AP delay would be largely determined by the electrical synapse, and should not be significantly affected by the chemical synapse. This result is well in line with the prevalence of electrical synapse in neural circuits responsible for a rapid response requiring behavior, such as escape reflexes (Allen, Godenschwege, Tanouye, & Phelan, 2006; Herberholz, Antonsen, & Edwards, 2002). Finally, we evaluated how different combinations of electrical and chemical synaptic conductances could affect the firing frequency of a postsynaptic neuron. Our data indicate that some combinations of synaptic conductances, provided by electrical and chemical NMDA synapses, could be most cost-efficient for ensuring the required firing rate in the postsynaptic neuron. In contrast, no such combination could be found for the mixed synapse containing an AMPA chemical synapse, due to concave shape of estimated isofrequency lines.

That is, either a purely chemical AMPA synapse or a purely electrical synapse was the most efficient in providing the required firing frequency. These results may provide at least a partial mechanistic explanation for the prevalence of mixed synapses containing NDMA synapse, as compared to other types of chemical synapses.

Material and methods

Membrane excitation

To simulate the transfer of electrical signal between neurons, connected through a mixed synapse, we adapted the standard Hodgkin-Huxley model (Hodgkin & Huxley, 1952). The membrane conductances of presynaptic and postsynaptic neurons were described by the following system of ordinary differential equations:

$$\begin{cases} C_1 \frac{dV_{m_1}}{dt} = I_1 - I_{Na_1} - I_{K_1} - I_{L_1} + I_{el_1} \\ C_2 \frac{dV_{m_2}}{dt} = I_2 - I_{Na_2} - I_{K_2} - I_{L_2} + I_{el_2} + I_{ch}. \end{cases}$$

Here, V_{m_1}, V_{m_2} – denotes membrane potentials of presynaptic and postsynaptic neurons, respectively (mV); C_1 ir C_2 – membrane capacity (μF/cm²); I_1, I_2 – external stimulating currents, applied to the presynaptic and postsynaptic neurons, respectively (mA/cm²); I_{Na_1} and I_{Na_2} – sodium currents (mA/cm²), I_{K_1} ir I_{K_2} – potassium currents (mA/cm²), I_{L_1} ir I_{L_2} – leakage currents (mA/cm²); I_{el_1} and I_{el_2} – transjunctional currents through an electrical synapse (mA/cm²); I_{ch} – current in the postsynaptic neuron, provided by an activation of a chemical synapse. In our simulations, we assumed that cells have the same surface area of $1.25 \cdot 10^{-5}$ cm². Parameters describing the membrane capacitance and ionic currents were the same as per original publication of the Hodgkin-Huxley model (Hodgkin & Huxley, 1952).

Electrical synapses

Most electrical synapses detected in mixed synapses, were formed of Cx36 and its orthologs (Hamzei-Sichani *et al.*, 2012; A. Pereda *et al.*, 2003). It is well established that Cx36 gap junction channels exhibit a very low sensitivity to transjunctional voltage (Srinivas *et al.*, 1999), therefore, in contrast to our previous modeling studies (Maciunas, Snipas, Paulauskas, & Bukauskas, 2016; Snipas, Rimkute, Kraujalis, Maciunas, & Bukauskas, 2017), we assumed that electrical synapses act as simple resistors. In that case, transjunctional currents could be described by the following equations:

$$I_{el_1} = g_{el}(V_{m_2} - V_{m_1});\ I_{el_2} = g_{el}(V_{m_1} - V_{m_2})$$

Here, g_{el} denotes the conductance of electrical synapse.

Chemical synapse

For simplicity, we assumed that concentration of neurotransmitter after an activation of chemical synapse can be described as a rectangular pulse (Destexhe, Mainen, & Sejnowski, 1994a):

$$[T] = \begin{cases} T_{max}, t_1 \le t \le t_1 + \Delta t; \\ 0, otherwise. \end{cases}$$

Here Δt denotes a short time interval (1 ms in our simulations), when concentration of neurotransmitter in a synaptic cleft is equal to the maximum concentration, $T_{max} = 1\ mM$; t_1 - activation of neurotransmitter release. It was assumed that neurotransmitter is released when an AP in a presynaptic neuron descends to -50 mV (Kaeser & Regehr, 2014).

The ratio of open receptor channels, r, was modeled by the following differential equation:

$$\frac{dr}{dt} = \alpha[T](1 - r) - \beta r;$$

Here, [T] denotes concentration of neurotransmitter at the receptor site; α – the opening rate of the receptor channel; β – closing rate of the receptor channel. These rate constants depend on the type of receptor, which defines the type of a respective chemical synapse. In our simulations, the values of rate constants α and β for different types of receptors were the same as provided in (Destexhe, Mainen, & Sejnowski, 1994b). The more detailed descriptions are provided below.

AMPA synapse

We used the following equation to describe an excitatory synaptic current, associated to AMPA receptor channels:

$$I_{ch} = r(t) \cdot g_{AMPA} \cdot (V_{m_2} - E_{AMPA});$$

Here, g_{AMPA} denotes the maximum synaptic conductance (nS), while E_{AMPA} is an equilibrium potential of AMPA receptors (0 mV).

NMDA synapse

The following equation was used to describe an excitatory synaptic current, associated to NMDA receptor channels:

$$I_{ch} = r(t) \cdot g_{NMDA} \cdot B(V_{m_2}) \cdot (V_{m_2} - E_{NMDA});$$

$$B(V_{m_2}) = \frac{1}{1 + e^{\frac{(-0.062 \cdot V_{m_2})[Mg^{2+}]_o}{3.57}}}.$$

Here, g_{NMDA} denotes the maximum synaptic conductance and E_{NMDA} – equilibrium potential of NMDA receptors (0 mV). $B(V_{m_2})$ is a function, describing the receptor blockage by extracellular Mg^{2+} ion concentration, $[Mg^{2+}]_o$ (1 mM in our simulations).

GABA$_A$ synapse

The following equation was used to describe an inhibitory synaptic current, associated to GABA$_A$ receptor channels:

$$I_{ch} = r(t) \cdot g_{GABA_A} \cdot (V_{m_2} - E_{GABA_A});$$

Here g_{GABA_A} denotes the maximum synaptic conductance (nS), while E_{GABA_A} – an equilibrium potential of GABA$_A$ receptor (-70 mV).

Numerical simulations

The mathematical models of neuronal excitation and synaptic currents were implemented in MATLAB. For numerical integration of differential equations we used the Euler method with time step of 0.01-0.001 ms.

Results and discussion

The effect of a mixed synapse, containing an inhibitory chemical synapse, on the membrane potential of a postsynaptic neuron

An activation of an inhibitory chemical synapse reduces membrane potential of a postsynaptic neuron, thus lowering the probability that it will generate an AP. We performed numerical simulations to compare the effect of electrical, inhibitory GABA$_A$ synapse and a mixed synapse, containing both electrical and chemical GABA$_A$ synapses.

Fig. 1A demonstrate the response in the postsynaptic neuron, cell-2, when the presynaptic neuron, cell-1, generates an AP, and both cells are connected through an electrical (left panel), an inhibitory GABA$_A$ (middle panel) or a mixed synapse (right panel). In this numerical experiment, cell-1 was stimulated by an external impulse of 2 ms in duration (starting from the 1st ms) and 52.5 pA in amplitude, which was sufficient to activate an AP in cell-1 (not shown). It can be seen that coupling provided by the electrical synapse generates a well-expressed biphasic response in the cell-2, while inhibitory GABA$_A$ synapse of the same conductance (1 nS) caused only a small IPSP. The right panel in Fig. 1A shows that the response enabled by the mixed synapse closely resembles that of the electrical synapse.

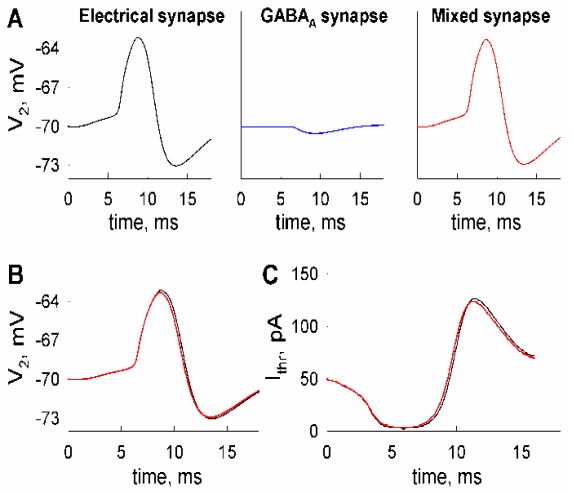

Fig. 1. The effect of a mixed synapse, containing an electrical and an inhibitory GABA$_A$ synapse. A) The kinetics of membrane potential in a postsynaptic neuron (V_2) connected to the presynaptic neuron through an electrical, an inhibitory GABA$_A$ or a mixed synapse, containing both electrical and chemical GABA$_A$ synapses. B) The overlay of V_2 exhibited by postsynaptic neuron, connected to either an electrical (black line) or the mixed (red line) synapse. C) The amplitude of an external current pulse (2 ms in duration), which would be sufficient to generate an AP in the postsynaptic neuron, when it is coupled to the presynaptic neuron be the mixed synapse. In all the presented examples, synaptic conductances of electrical and chemical synapses, g_{el} and g_{chem}, respectively, were both equal to 1 nS.

Fig. 1B shows two overlays of the responses in the postsynaptic neuron, when both cells were coupled through the electrical or the mixed synapse (black and red lines, respectively). It can be seen, that these responses basically overlap, and very small differences can only be observed in a relatively short (~3 ms) time-window.

To evaluate this additional inhibitory effect provided by the $GABA_A$ synapse in a more detailed way, we estimated amplitudes of an external current pulse (2 ms in duration), which would be required to generate an AP in the postsynaptic neuron at different time moments. In this numerical experiment, the postsynaptic neuron was affected by an AP incoming from the presynaptic neuron, as well as from the external stimulation. Fig. 1C shows that these threshold currents are basically the same, whether neurons are connected by either an electrical or by a mixed synapse, containing an inhibitory $GABA_A$ synapse. Thus, an addition of GABAergic synaptic connection to electrically coupled neurons should not significantly affect the response of the presynaptic neuron, at least when both electrical and chemical synaptic components are of similar conductances.

Overall, the obtained simulation results indicate that connecting a pair of neurons by an inhibitory $GABA_A$ synapse, which are already coupled through an electrical synapse of comparable conductance, should not affect the response in postsynaptic neuron significantly. That is, an IPSPs provided by a chemical synapse would be overwhelmed by an inhibitory phase of the biphasic response incoming to the postsynaptic neuron through the electrical synapse. Presumably, this could explain the fact that almost none of the mixed synapses, thus far detected in animal tissues, contained inhibitory synapses.

The effect of a mixed synapse, containing an excitatory chemical synapse, on the membrane potential of a postsynaptic neuron

In contrast to inhibitory synapses, an activation of excitatory chemical synapse raises the membrane potential of a postsynaptic neuron, thus increasing the probability that it will generate an AP.

To evaluate the combined effect of electrical and excitatory chemical synapses, we performed numerical experiments between two cells, connected through an electrical, an excitatory chemical (either AMPA or NMDA) or a mixed synapse, containing both synaptic connections.

First, we wanted to evaluate the effect these types of synapses would have on the velocity of signal transfer between connected neurons.

The rapid transition of electrical signal is crucial for neuronal circuitry, regulating rapid response requiring behavior, such as escape reflexes, and it is well established that electrical synapses play an important role in these structures (Allen, Godenschwege, Tanouye, & Phelan, 2006; Herberholz, Antonsen, & Edwards, 2002).

Interestingly, mixed synapses, containing an excitatory chemical synapse, have also been detected in circuits regulating escape behavior, most notably, at the club endings of Mauthner cell of the goldfish (Lin & Faber, 1988; A. E. Pereda *et al.*, 1995; Tuttle *et al.*, 1986). Thus, we evaluated and compared the delays between APs in the pre- and postsynaptic neurons coupled through these types of synapses.

Fig. 2A shows APs generated in two neurons, connected through an electrical synapse (upper panel) and a mixed synapse containing an AMPA synapse (lower panel). In these computational experiments, the presynaptic neuron was stimulated by an external current pulse of 125 pA in amplitude and 2 ms, and the generated AP was transferred from the presynaptic to the postsynaptic neuron through the respective synaptic connection(s).

In these experiments, the electrical and chemical synapses exhibited equal conductances (1 nS). Fig. 2A shows that only a slight reduction in AP delay can be observed when the postsynaptic neuron exhibits an additional postsynaptic connection provided by the AMPA synapse. A mixed synapse, containing an NMDA synapse, provided the same delays between APs as a single electrical synapse (not shown).

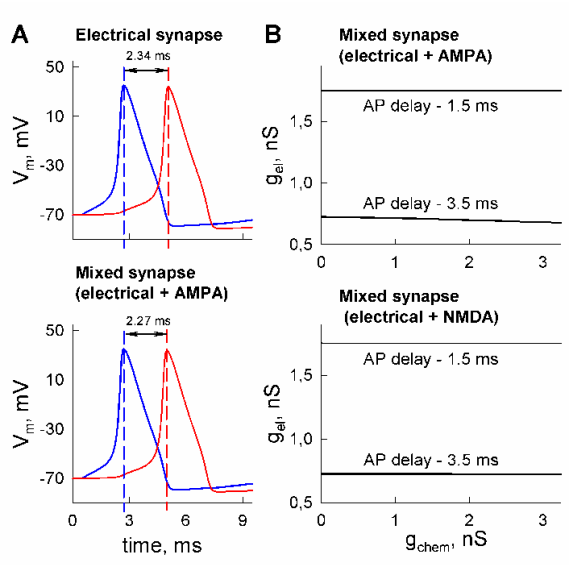

Fig. 2. The effect of a mixed synapse, containing an electrical and an excitatory AMPA or NMDA synapses, on the transfer of electrical signal between neurons. A) The membrane voltages (V_m) of the presynaptic (blue line) and the postsynaptic (red line) neurons, coupled through an electrical (upper panel) or a mixed (lower panel) synapse, containing a chemical AMPA synapse. Dashed vertical lines illustrate the resulting delay between APs. Conductances of electrical and chemical synapses, g_{el} and g_{chem}, were both equal to 1 nS. B) The mixtures of g_{el} and g_{chem} which would be required to ensure 1.5 or 3.5 ms delay between the presynaptic and postsynaptic neurons. Neurons were connected through a mixed synapse, which contains an AMPA (upper panel) or an NMDA (lower panel) synapse.

For a more comprehensive evaluation of the velocity of electrical signal transfer, we estimated the minimum conductances of electrical and chemical components, which would be sufficient to ensure the required delay (1.5 mS or 3.5 ms) between APs. Fig. 2B shows these results for mixed synapses, containing an AMPA (upper panel) or an NMDA (lower panel) chemical synapse. The obtained curves are almost parallel to g_{chem} axis, which means an extremely low variation in g_{el}, compared to g_{chem}, at least in the physiological ranges of g_{chem} (Li & Gulledge, 2021). This shows that the required delay is mostly determined by the electrical synaptic conductance, and a very rapid response in the postsynaptic neuron could only be ensured by the electrical synapse.

Overall, the data indicate that the speed of signal transfer between two neurons, connected through a mixed synapse, would be mainly determined by the electrical synapse, and could only marginally be affected by the activation of the excitatory chemical synapse. These results are well in line with the fact, that electrical mode of synaptic transmission dominates in neural circuits, controlling rapid response requiring behavior.

The effect of mixed synapse, containing excitatory chemical synapse, on the firing frequency of postsynaptic neuron

Firing frequency is one of the most important characteristics of neuronal networks, because it is widely considered that neurons code and process information through the changes of its firing rates (Gerstner, Kreiter, Markram, & Herz, 1997). However, maintaining high frequency rate is energetically costly, and it is one of the main reasons for disproportionally high amount of energy, consumed by the functioning brain. For example, it was estimated that human brain represents only ~2 percent of body mass, but it consumes ~20 percent of energy, most of it by neurons (Raichle & Gusnard, 2002). To evaluate how firing frequency is affected by mixed synapses, and what proportions of electrical and excitatory chemical conductances would be most efficient in this regard, we performed detailed numerical experiments. In these simulations, the presynaptic neuron was stimulated by a long step of an external current which was sufficient to drive the series of APs in the presynaptic neuron. The resulting firing rate in the postsynaptic neuron was estimated for different combinations of electrical and chemical synaptic conductances, g_{chem} and g_{el}, respectively.

Fig. 3A shows a few examples of the obtained isofrequency contours. It can be seen that isolines of a mixed synapse, containing an AMPA chemical synapse, exhibit a regular concave shape, while the respective contours for the mixed synapse, containing an NMDA synapse, are somewhat irregular and possess inflection points. These differences can have important implications if one considers an optimal combination of conductances of electrical and

chemical synapses to ensure the required frequency. For example, suppose that "costs" (from the perspective of an organism) associated with the maintenance of a mixed synapse is described by the following function:

$$C = C_{chem} \cdot g_{chem} + C_{el} \cdot g_{el}$$

Here, the coefficients C_{chem} and C_{el} reflect costs, which would be necessary to maintain the unit of g_{chem} and g_{el}, respectively. Presumably, these costs would reflect the amount of metabolites and/or ATP molecules necessary to build the respective synapse and to maintain its functionality. Of course, it would be very difficult to estimate the exact costs of C_{chem} and C_{el}, however, such approach still allows for some theoretical considerations. That is, the optimal solution C_{min} would be an intersection point of the line $C_{el} \cdot g_{el} + C_{chem} \cdot g_{chem} = C_{min}$ and the respective isofrequency contour. For concave contour lines, such as those describing isofrequencies of the mixed synapse containing AMPA repectros (left panel in Fig. 3C), the minimum value of the cost function, C_{min}, would be provided by either g_{el} = 0 or g_{chem} = 0 nS, independently on the C_{el} /C_{chem}, which determines the slope of the linear cost function (see left panel in Fig. 3B). This means that a purely electrical or a purely chemical synapse should always be more cost-efficient than a mixed synapse, in maintaining the respective firing rate. However for an NMDA synapse, it is possible to find a ratio C_{el}/C_{chem} which would yield the minimum point, in which both g_{el} > 0 and g_{chem} > 0 nS. That is, a mixed synapse would provide an optimal combination of synaptic conductances. The right panel in Fig. 3B shows such an example, when g_{el} = 0.64 and g_{chem} = 0.87 provides an optimal mixture of synaptic conductances to ensure the required 20 Hz frequency.

In the hypothetical scenario, presented in Fig 3B, the cost of a chemical synapse is much lower compared to the electrical synapse (i.e., C_{el}/C_{chem} = 12). Such an assumption is not inconceivable if one considers the hypothetical occurrence of a mixed synapse during the course of evolution. The evidence show that both electrical and chemical modes of signal transfer have coexisted independently from each other for millions of years (Ovsepian & Vesselkin, 2014). Assuming that by some random mutation an electrical synapse was inserted near a chemical synapse, i.e., at a structure which is already adapted to maintain chemical mode of transduction, it would be very likely that C_{el} for a newly inserted electrical synaptic connection would be much higher than C_{chem} for an existing chemical connection. However, the resulting combined effect obtained by such a mixed synapse could ensure some type of competitive advantage, thus maintaining it for further generations.

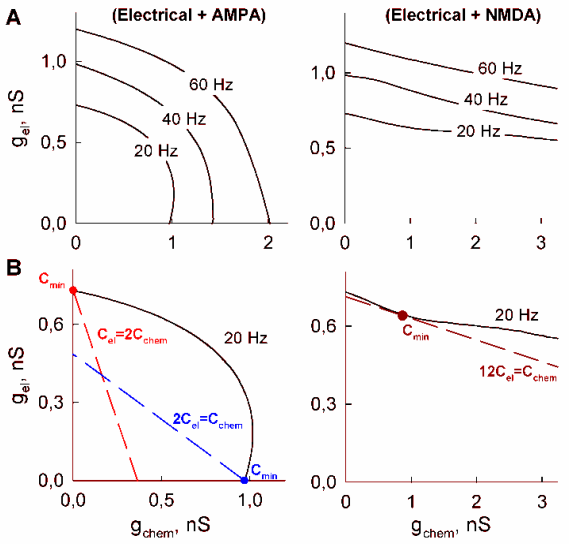

Fig. 3. The effect of chemical and electrical conductances for the firing rate of the postsynaptic neuron. A) The isofrequency contour lines, showing the mixtures of synaptic conductances provided by a chemical (AMPA in the left panel, and NMDA in the right panel) and an electrical synapses, g_{chem} and g_{el}, respectively, which would ensure the required firing rate in a postsynaptic neuron. B) An example of optimization task, for finding an optimal combination of g_{chem} and g_{el} to maintain 20 Hz firing rate in the postsynaptic neuron. The left panel shows that when g_{chem} is provided by an AMPA synapse, the minimum of the cost function ($C_{chem} \cdot g_{chem}$ + $C_{el} \cdot g_{el}$) would be obtained at either g_{chem}=0 (i.e., a purely electrical synapse) or g_{el}=0 (i.e., a purely chemical synapse). In contrast, the right panel shows that it is possible to obtain the scenario in which both g_{chem}>0 and g_{el}>0, which means that a mixed synapse would be the most efficient for the maintenance of the required firing rate, if it contained an NMDA synapse.

Conclusions

Our computational modeling data revealed that in a mixed synapse, containing an inhibitory GABA synapse, it would be unlikely for IPSPs, generated by the chemical synapse, to significantly affect the firing rate of the postsynaptic neuron. This could be explained by the fact, that IPSPs to a large extent would be obscured by the biphasic response generated by an electrical synapse. We suggest that it might provide a mechanistic explanation for the scarcity of evidence for the existence of mixed synapse containing GABAergic inhibitory synapses. In addition, our simulation data show that the delay between APs in two neurons connected through a mixed synapse, containing an excitatory chemical synapse, would be mostly determined by an electrical component. Thus, it is unlikely that the main function of a chemical component in a mixed synapse would be related to an increased velocity of signal transfer in an anterograde direction. Finally, the analysis of firing rate of the postsynaptic neuron showed that in the majority of cases, the most efficient combinations of electrical and chemical synaptic conductances would be provided by either a purely electrical or a purely chemical synapse. However, for NMDA (but not for AMPA) synapses we were able to identify some combinations of electrical-chemical synaptic conductances, which would be the most efficient with respect to the maintenance of the required firing rate in the postsynaptic neuron. These results are in line with empirical evidence on the relative scarcity of mixed synapses among all possible synaptic connections, as well as for the fact that most of the mixed synapses, thus far detected in animal tissues, contained excitatory NDMA synapses (Bardoni *et al.*, 1998; Hamzei-Sichani *et al.*, 2012; Kamasawa *et al.*, 2006; Rash *et al.*, 2005).

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